Holger Schünemann, MD, MSc, PhD, FRCP(C)

Chair and Professor

Department of Health Research Methods, Evidence and Impact

McMaster University

Michael G. DeGroote COCHRANE CANADA CENTRE

GRADE working group

June 4, 2019 | NAS Workshop on Evidence Integration

Clinical Research Applications: Influenza Virus Drugs

@schunemann_mac

Disclosures

Cochrane Canada - Director

GRADE working group Co-Chair

Guideline International Network - committees

No direct financial COI

Views expressed my own

Overview

Clinical & Public Health Examples of Evidence integration

- How to integrate
- Human, animal, "mechanistic" evidence - rapid
- Recommendation about use

Goal of systematic reviews

Identify the best quality evidence to support a conclusion:

Exposure/intervention X increases/decreases outcome Y – high certainty

2005/6

World Health Organization had just undergone a review of its guideline methods

Health Research Policy and Systems

WHO

BioMed Central

Review

Open Access

Improving the use of research evidence in guideline development: introduction

Andrew D Oxman*[1], Atle Fretheim[1], Holger J Schünemann[2] and SURE[3]

Published: 21 November 2006

Health Research Policy and Systems 2006, **4**:13 doi:10.1186/1478-4505-4-13

Received: 07 April 2006

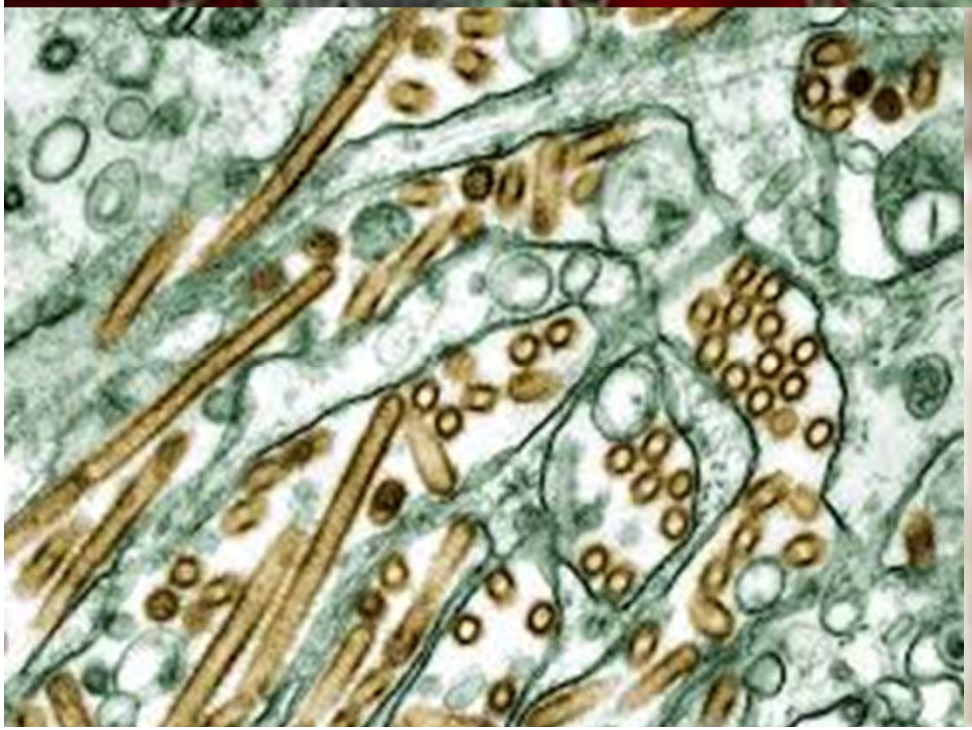
Accepted: 21 November 2006

This article is available from: http://www.health-policy-systems.com/content/4/1/13

Conclusion: WHO needs to use evidence, synthesized in systematic reviews, for its guidelines

Avian Influenza threat (H5N1) ~ 200 documented cases of transmission from birds to humans

WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus



Influenza A Virus

Divided into subtypes on the basis of two proteins on the surface of the virus:

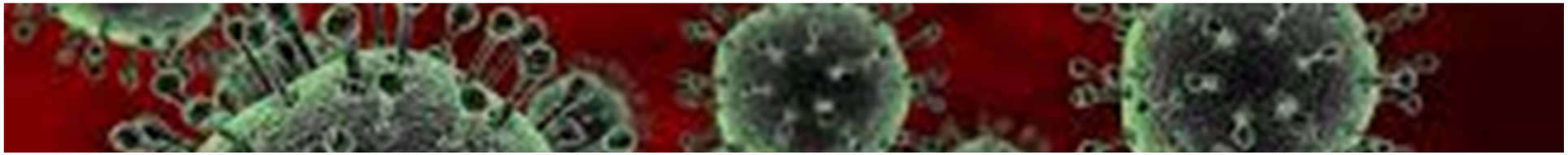
- hemagglutinin (HA) and neuraminidase (NA).
- 18 known HA subtypes and 11 known NA subtypes.
- Many different combinations of HA and NA proteins are possible.
- “H7N2 virus” designates an influenza A virus subtype that has an HA 7 protein and an NA 2 protein.
- “H5N1” virus has an HA 5 protein and an NA 1 protein.
- Different strains (e.g. H1N1 changed in 2009)

CDC website 2019

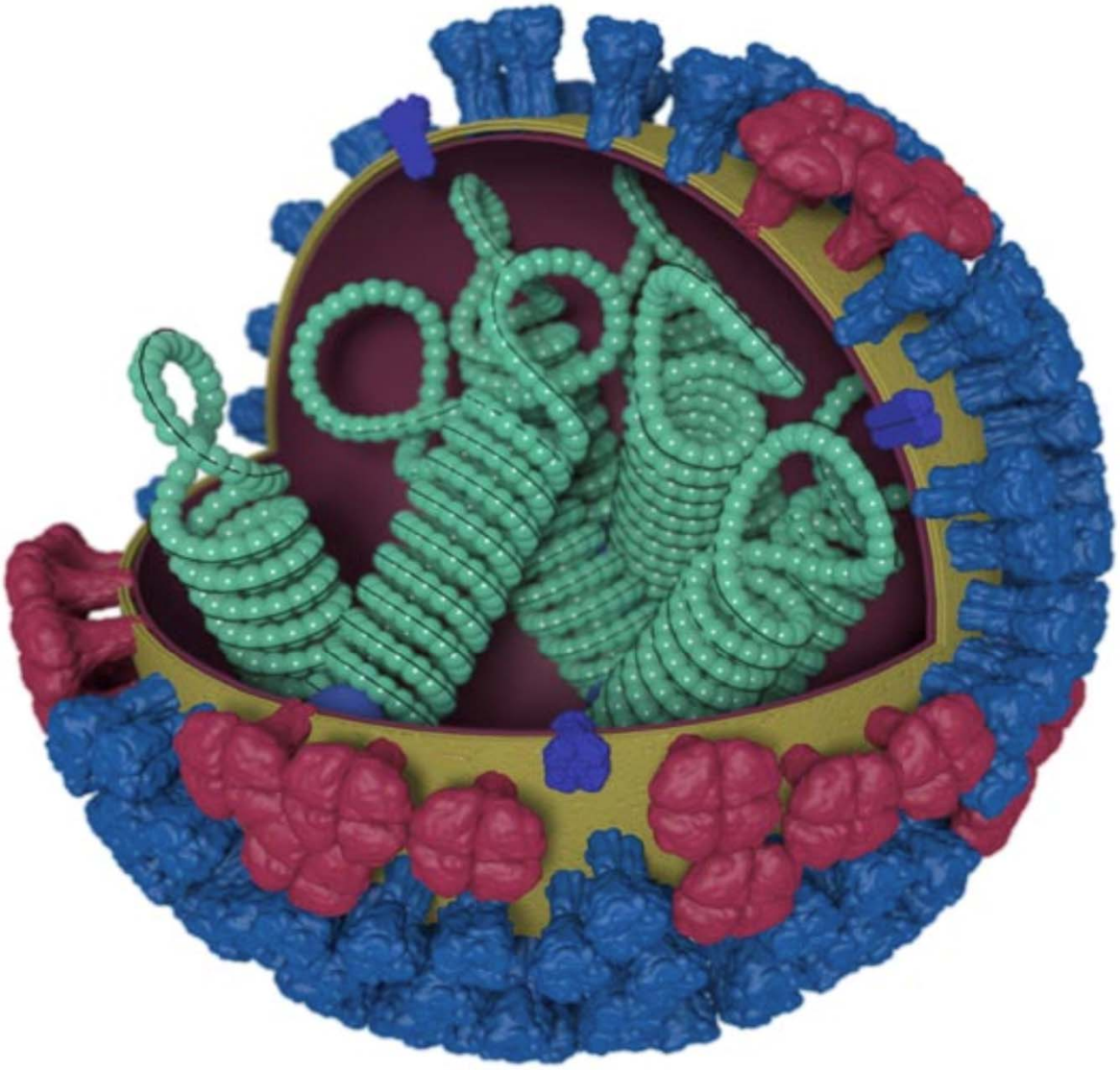
Avian influenza A (H5N1)

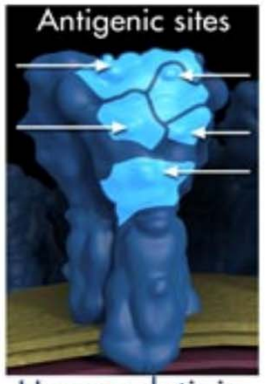
- Powerful virus, spread by migratory birds
- Kills 60%
- Transmits from birds to humans and indications for human to human transmission
- Sporadic human cases, but potential for human pandemic
- Agreement to stockpile antivirals, but no EB guidelines
- Treatment used for regular flu good for H5N1?

- Should oseltamivir be used for treatment of H5N1 in affected adults?

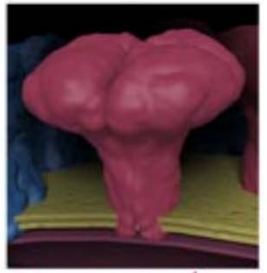


AN INFLUENZA VIRUS

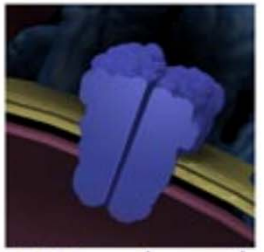




Hemagglutinin



Neuraminidase



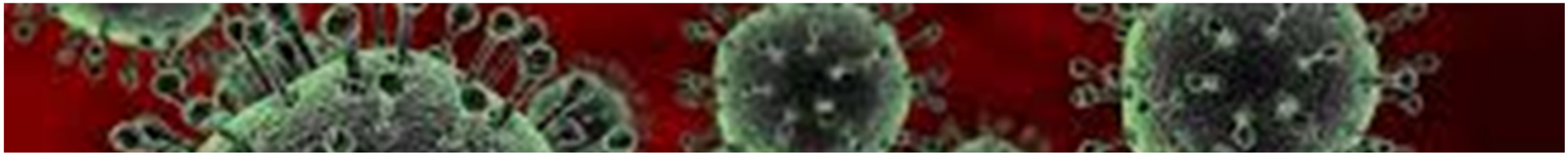
M2 ion channel

Ribonucleoprotein

CDC website 2019

PICO

Population:	Avian Influenza (H5N1) patients
Intervention:	Oseltamivir
Comparison:	No oseltamivir
Outcomes:	Mortality, hospitalizations, adverse outcomes, antimicrobial resistance



WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetali Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjdaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections with H5N1 virus worldwide. Despite international agreement to stockpile antivirals, evidence-based guidelines for their use do not exist. WHO assembled an international multidisciplinary panel to develop rapid advice for the pharmacological management of human H5N1 virus infection in the current pandemic alert period. A transparent

Lancet Infect Dis 2007; 7: 21–31

Italian National Cancer Institute Regina Elena, INFORMA Unit, Department of

OPEN ACCESS Freely available online

PLoS MEDICINE

Health in Action

Transparent Development of the WHO Rapid Advice Guidelines

Holger J. Schünemann*, Suzanne R. Hill, Meetali Kakad, Gunn E. Vist, Richard Bellamy, Lauren Stockman, Torbjørn Fosen Wisløff, Chris Del Mar, Frederick Hayden, Timothy M. Uyeki, Jeremy Farrar, Yazdan Yazdanpanah, Howard Zucker, John Beigel,

The best evidence – from systematic review(s)

No RCTs in humans infected with H5N1

One case series with 37 patients

- Direct (population)

5 RCTs in seasonal influenza

- Indirect (population)

Animal studies

In vitro

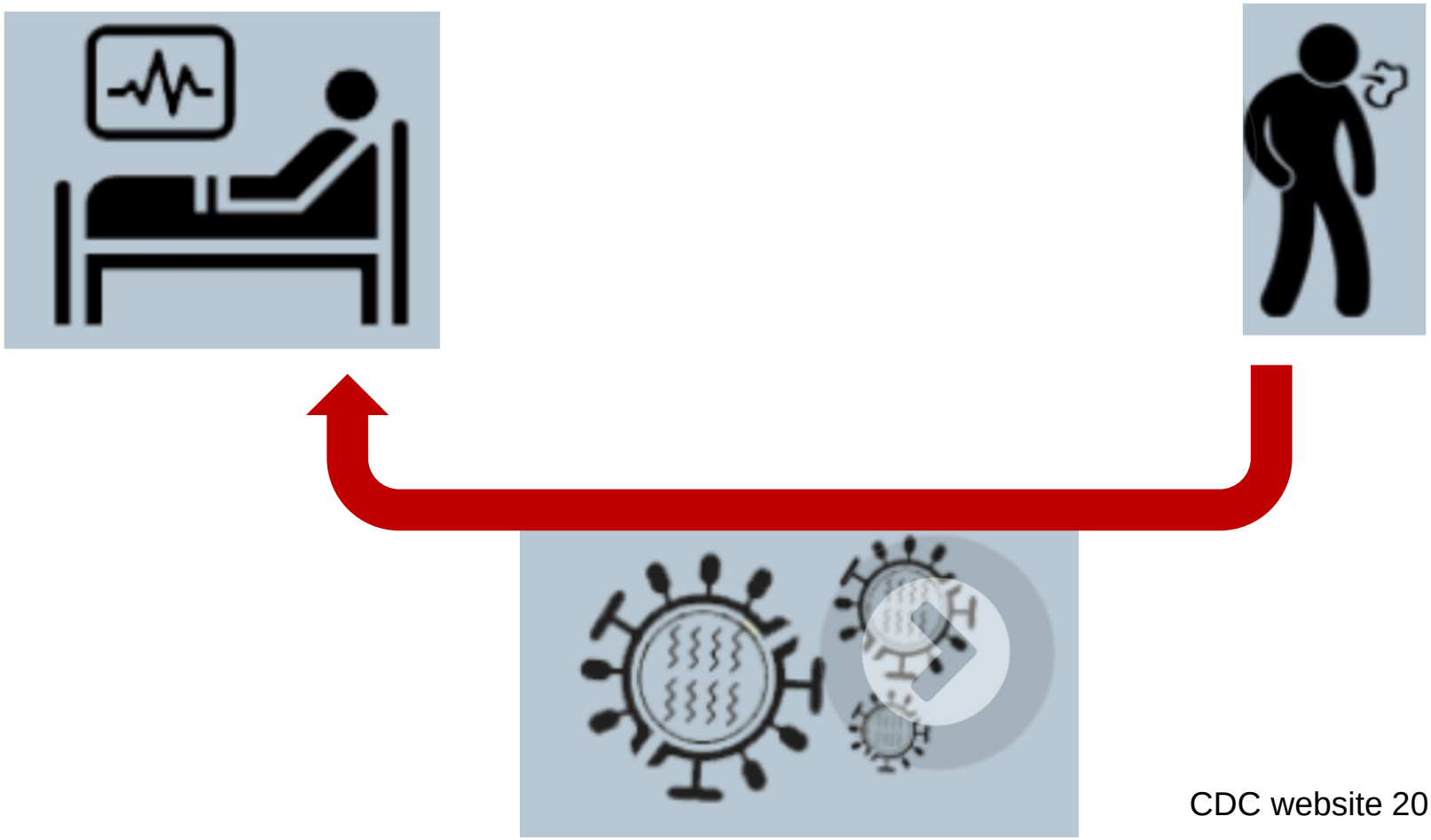
The best evidence

The existing evidence is based on small observational case series of H5N1 patients, results from in vitro and animal model studies of H5N1, or the extrapolation of data from high quality studies conducted to evaluate the treatment and chemoprophylaxis of normal, or “seasonal”, influenza

Similar enough for treatment to have similar effects?

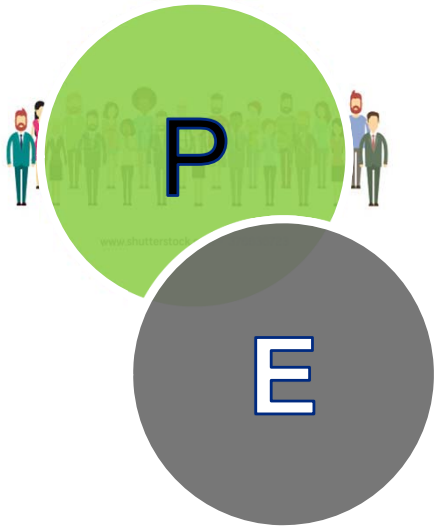
H5N1

H1N1 etc



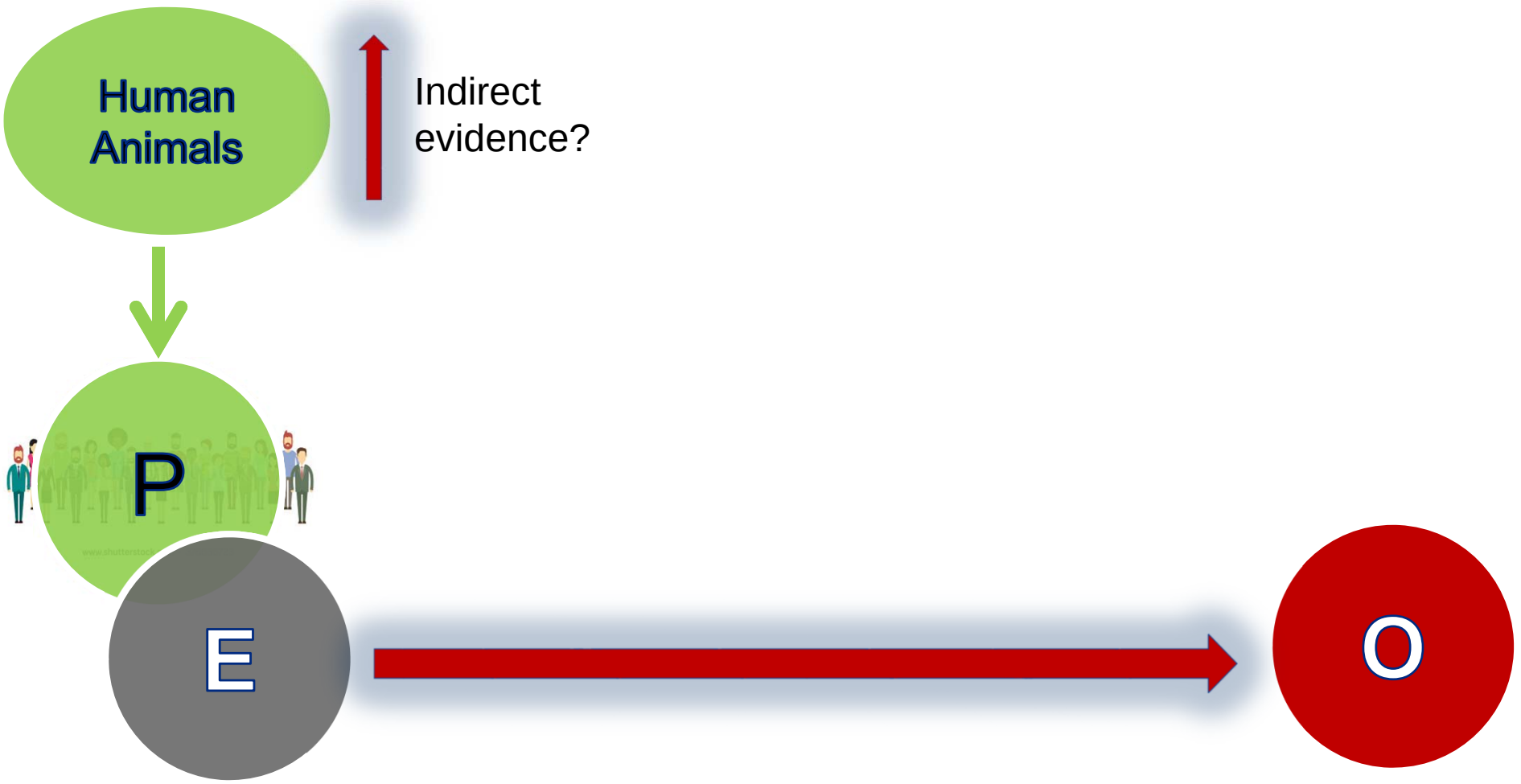
CDC website 2019


P

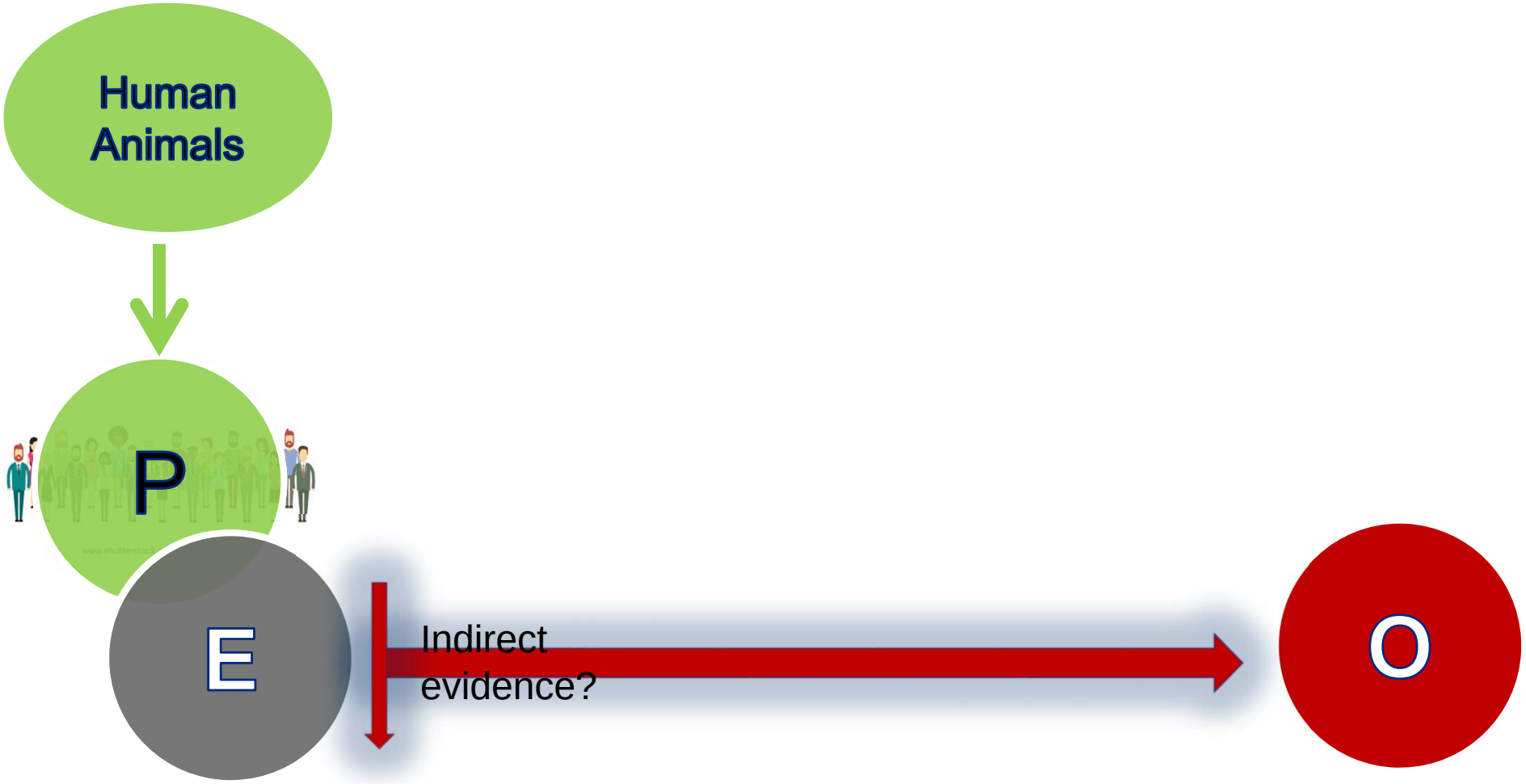

P
E


P
E
O

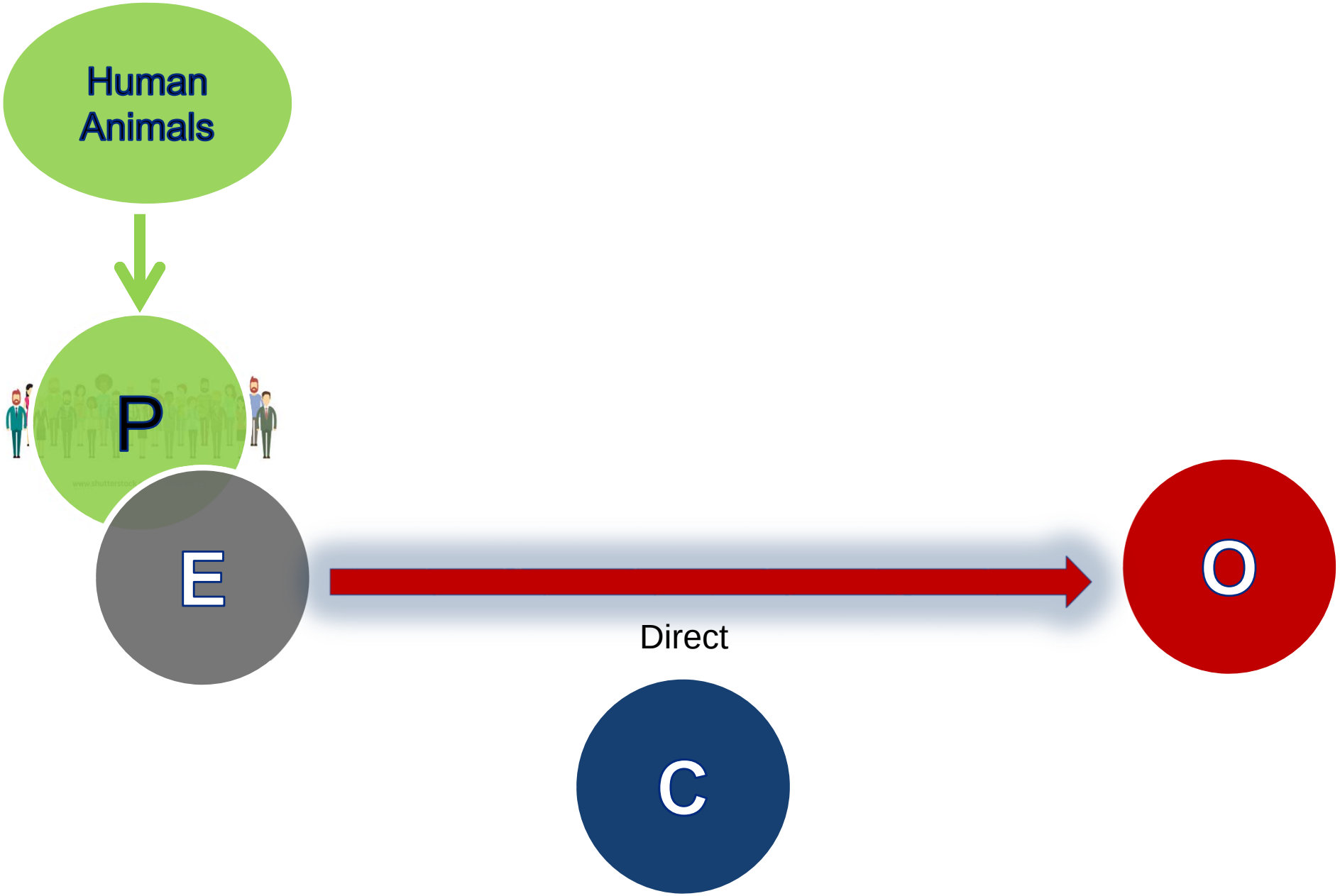

Human
Animals
P
E
O

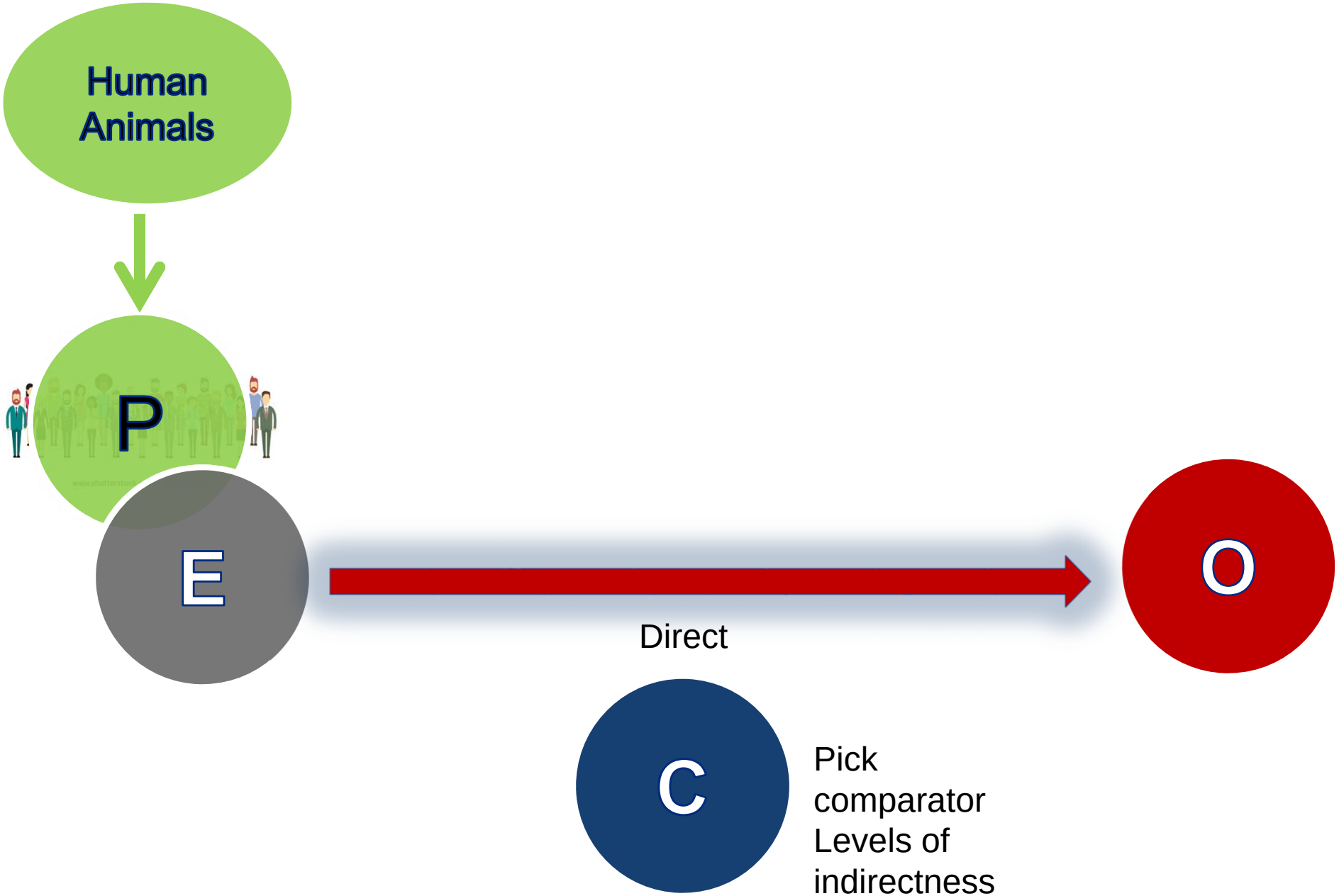

Human
Animals
Indirect
evidence?
P
E
O

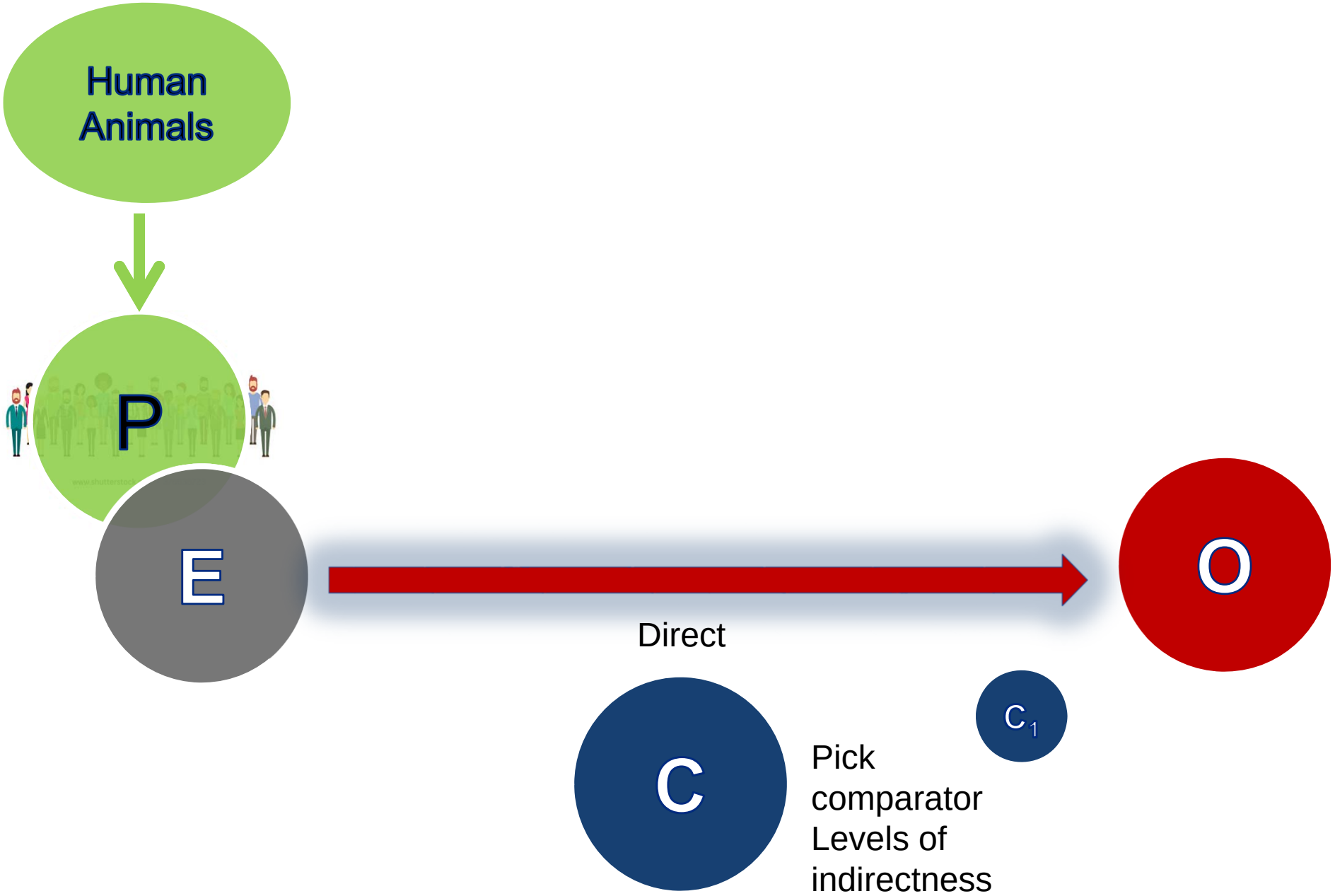

Human
Animals
P
E
O

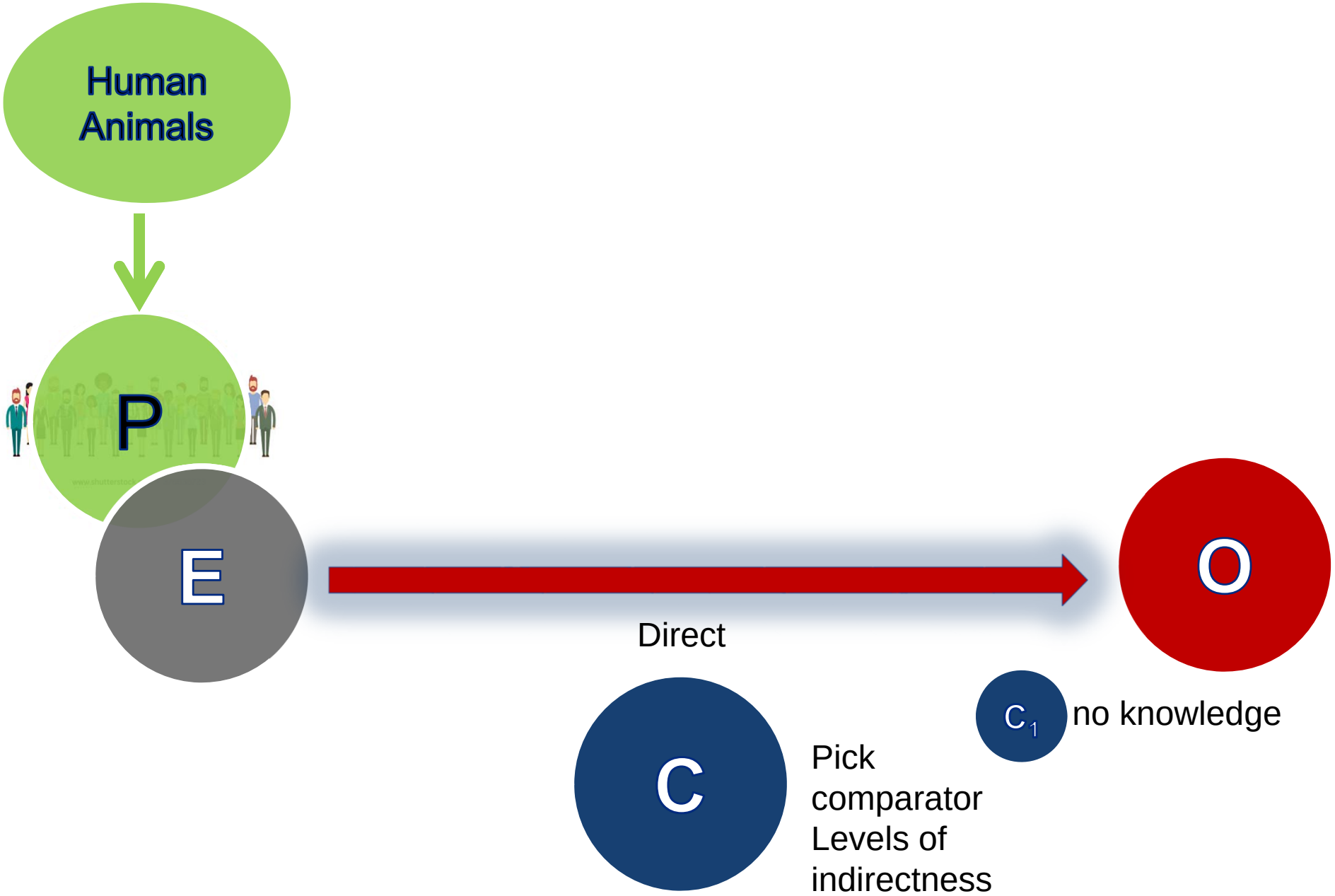

Human
Animals
P
E
Indirect
evidence?
O

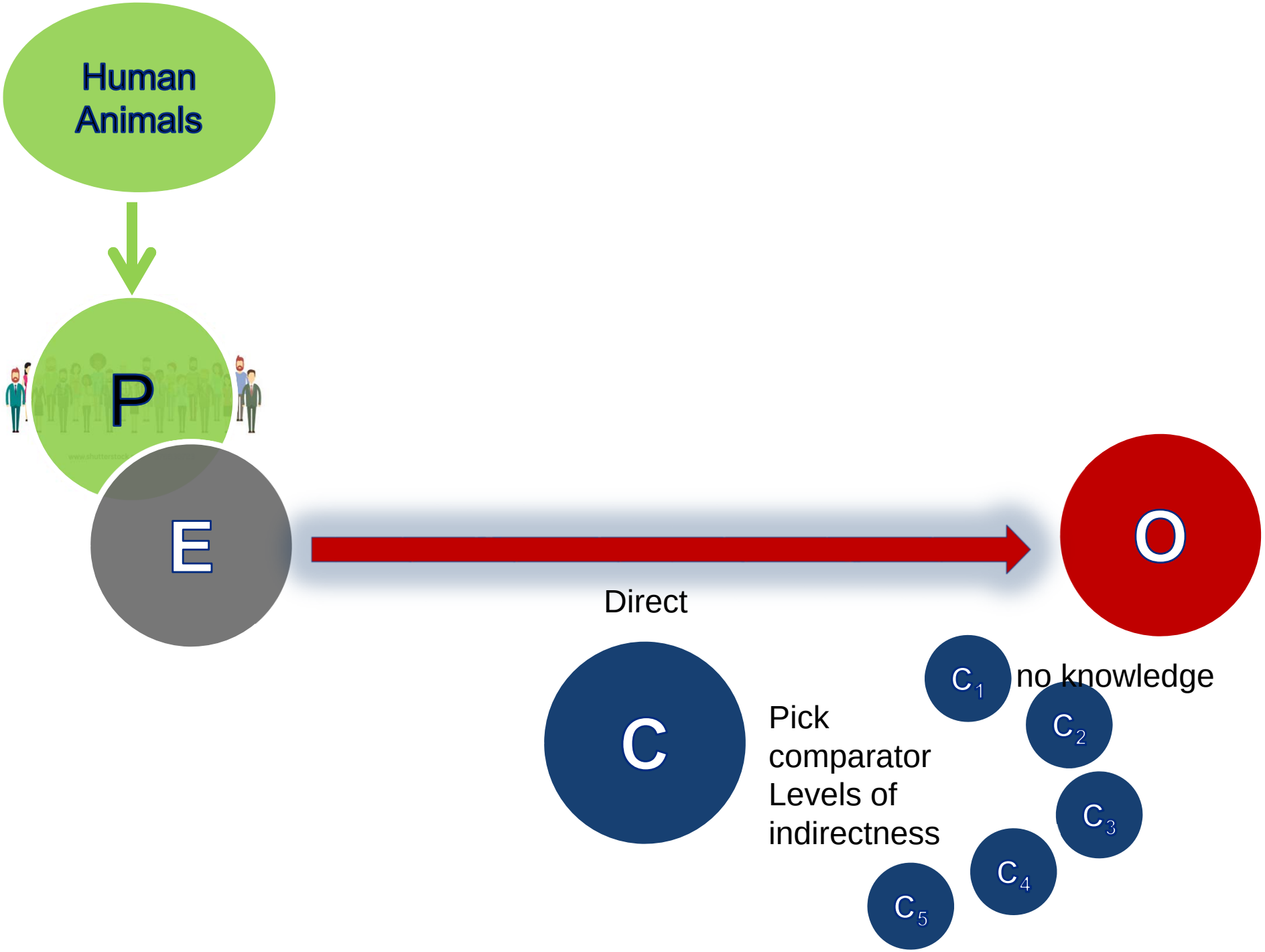

Human
Animals
P
E
O

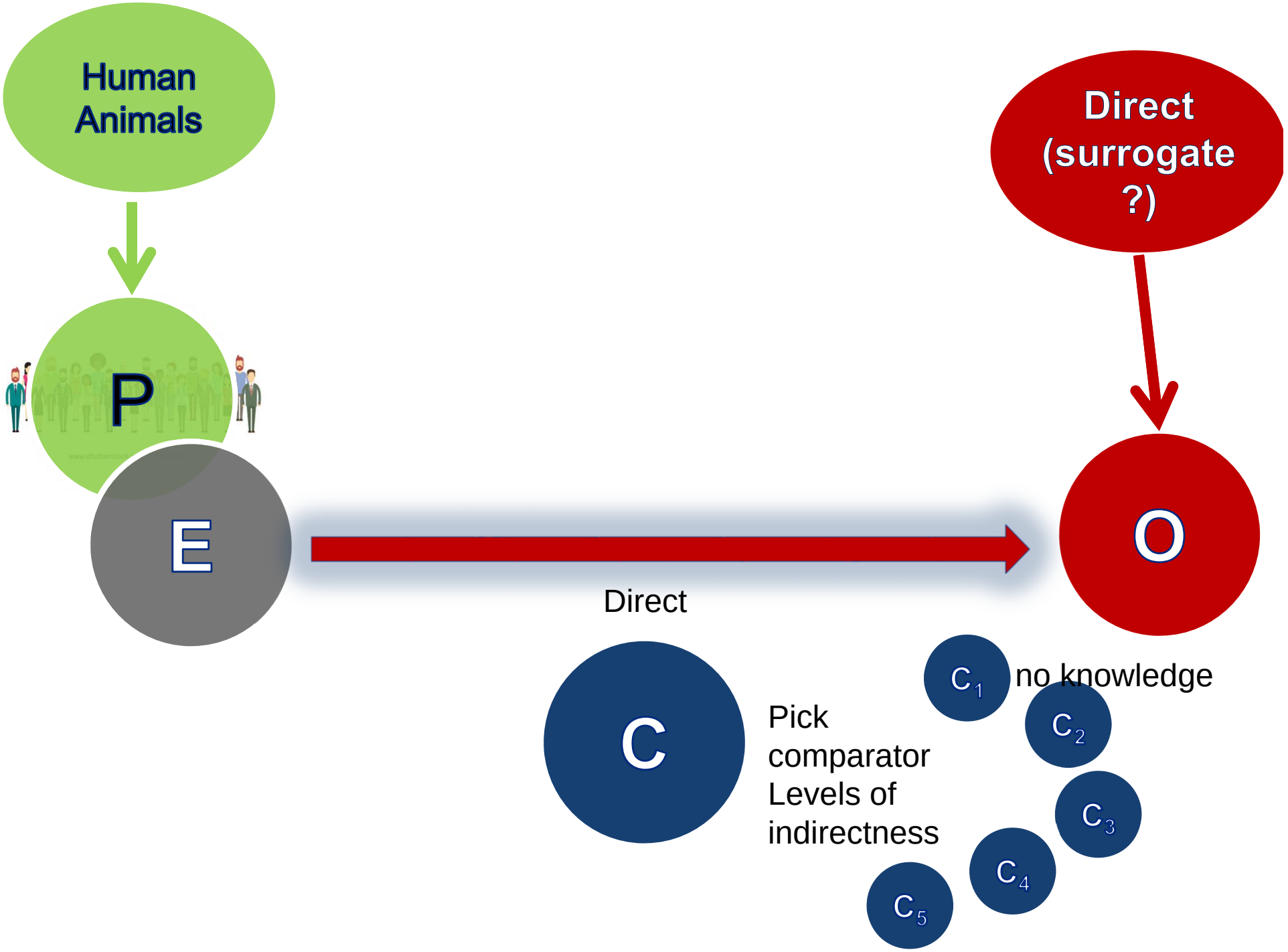

Human
Animals
P
E
O
Direct
C

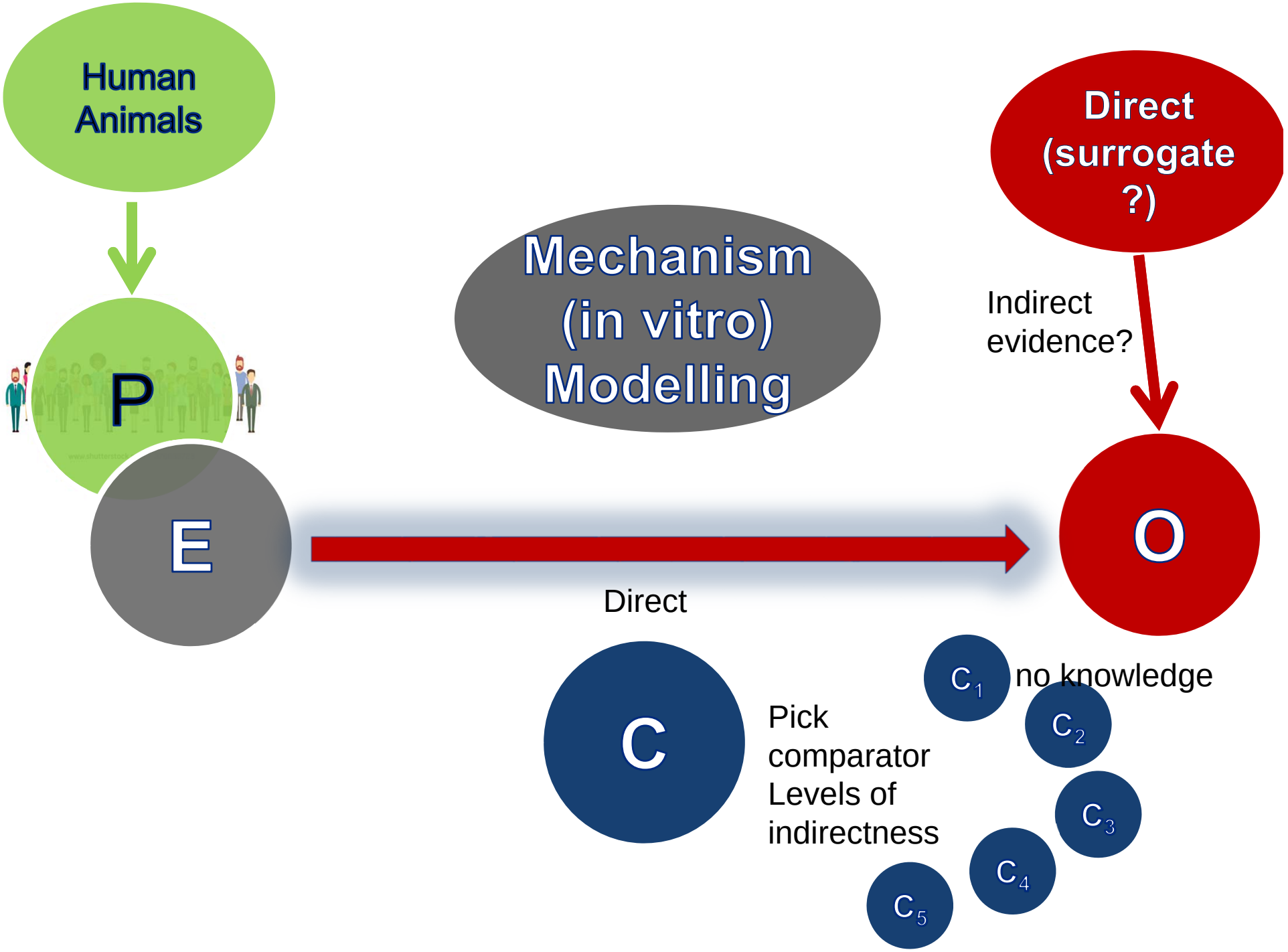

Human
Animals
P
E
O
Direct
C
Pick
comparator
Levels of
indirectness

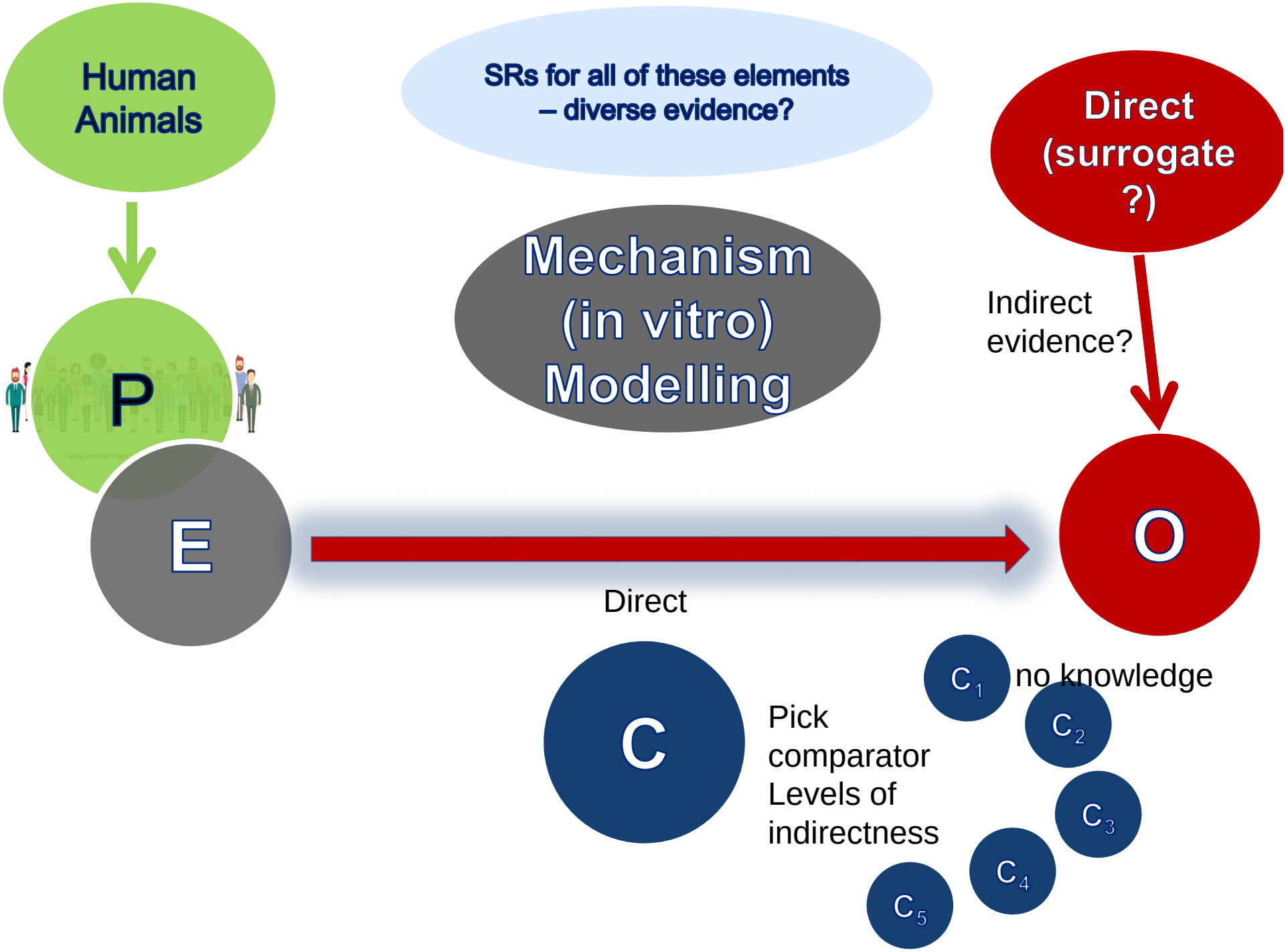

Human Animals
P
E
O
Direct
C
C_1
Pick comparator Levels of indirectness

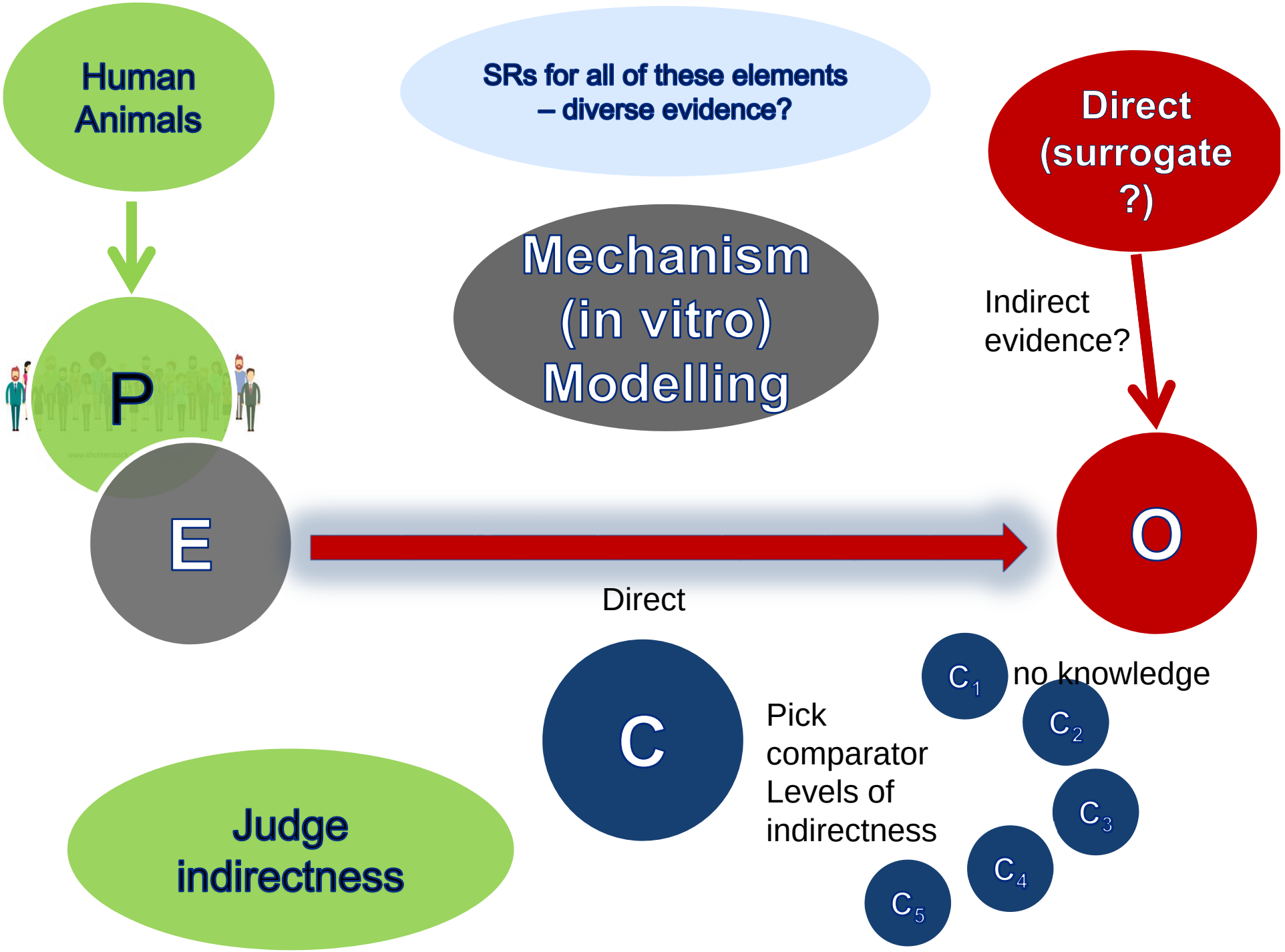

Human
Animals
P
E
O
Direct
C
Pick
comparator
Levels of
indirectness
C1
no knowledge

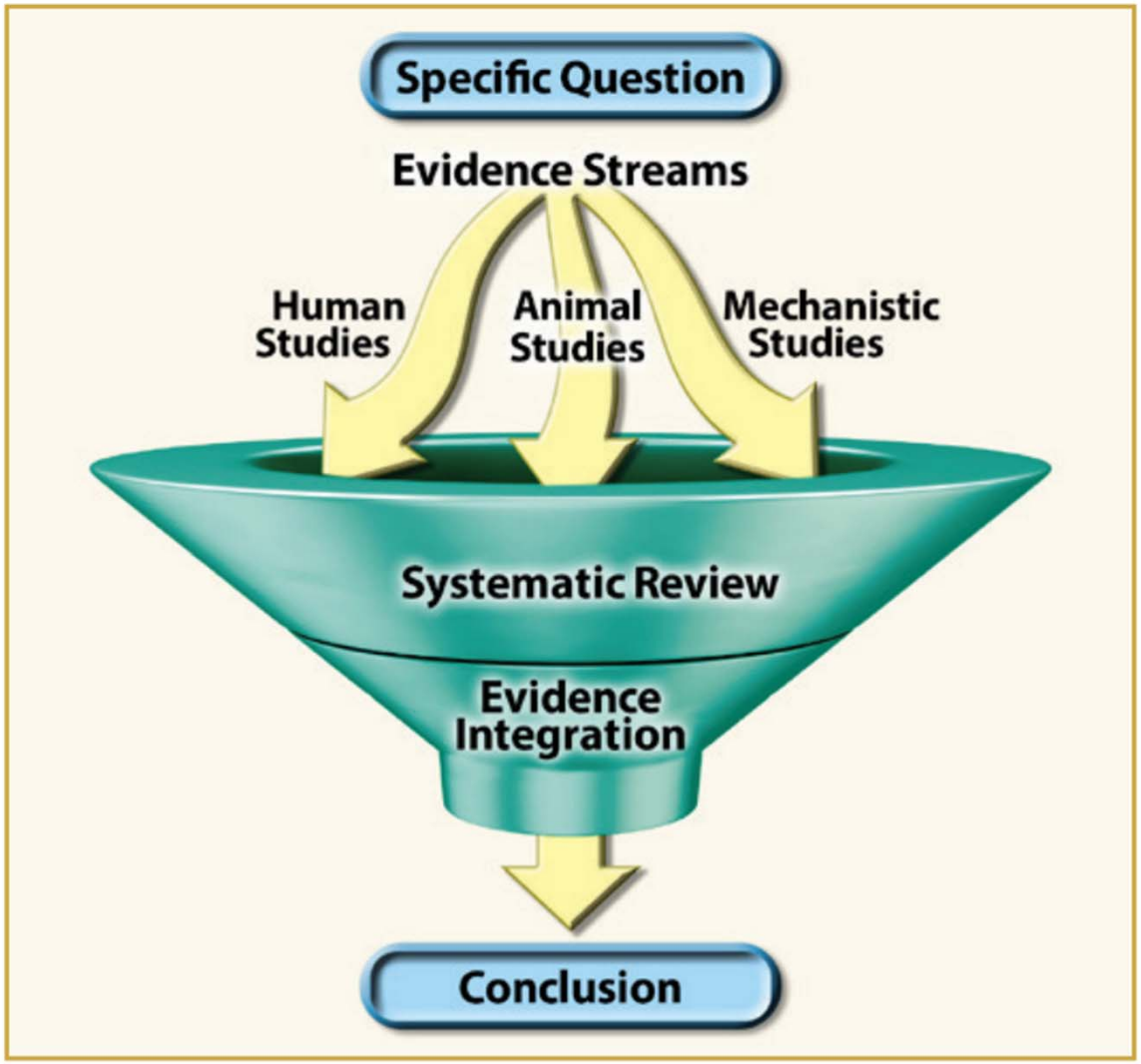

Human Animals
P
E
O
Direct
C
Pick comparator Levels of indirectness
C1
no knowledge
C2
C3
C4
C5


Human Animals
Direct (surrogate ?)
P
E
O
Direct
C
Pick comparator Levels of indirectness
C1
no knowledge
C2
C3
C4
C5


Human
Animals
P
E
Mechanism
(in vitro)
Modelling
Direct
(surrogate
?)
Indirect
evidence?
O
Direct
C
Pick
comparator
Levels of
indirectness
C1
no knowledge
C2
C3
C4
C5


Human Animals
SRs for all of these elements – diverse evidence?
Direct (surrogate ?)
Mechanism (in vitro) Modelling
Indirect evidence?
P
E
O
Direct
C
Pick comparator Levels of indirectness
C1
no knowledge
C2
C3
C4
C5


Human Animals
SRs for all of these elements – diverse evidence?
Direct (surrogate ?)
Mechanism (in vitro) Modelling
Indirect evidence?
P
E
O
Direct
C
Pick comparator Levels of indirectness
C1
no knowledge
C2
C3
C4
C5
Judge indirectness

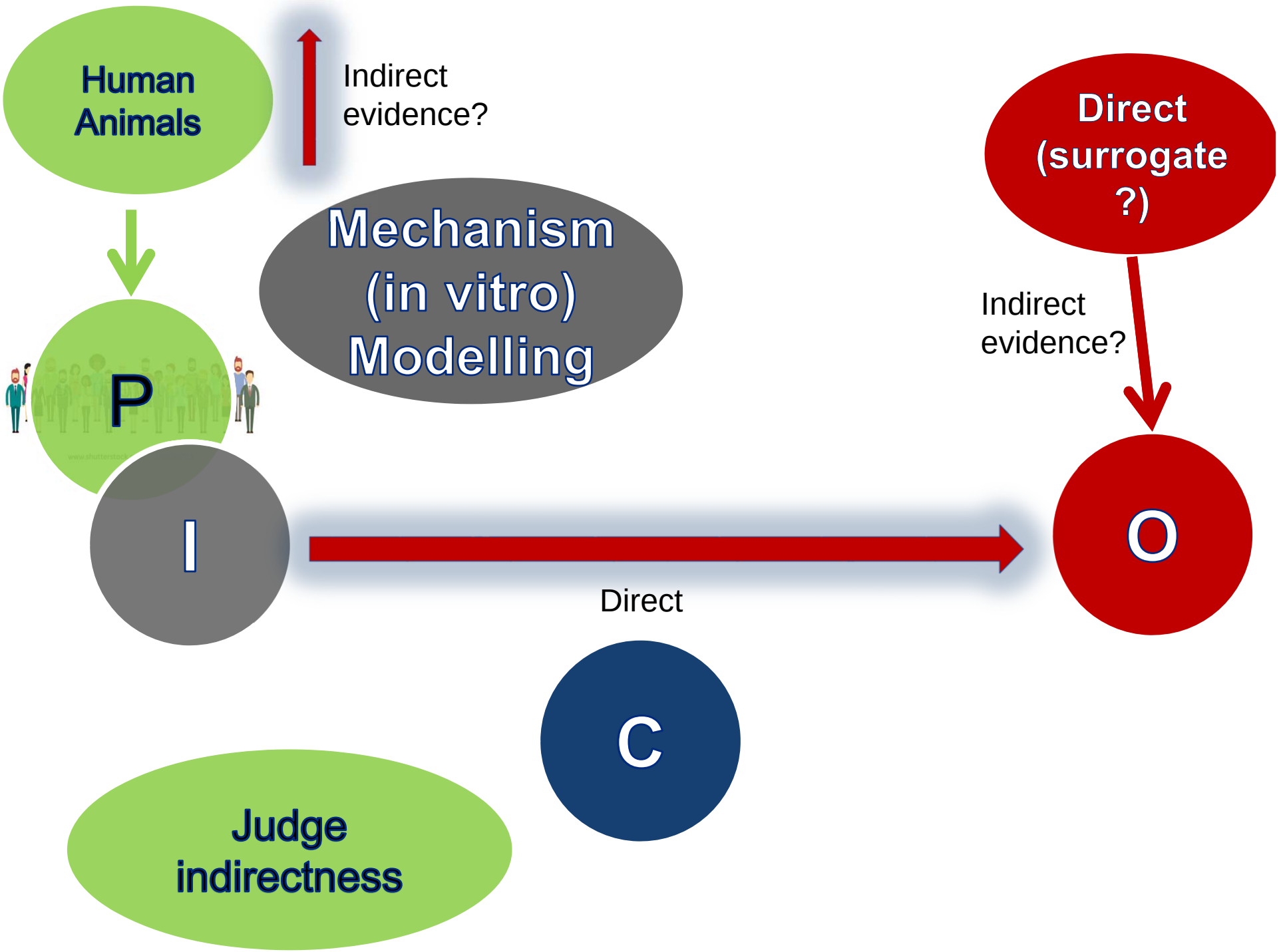


National Toxicology Program
U.S. Department of Health and Human Services

Mechanistic data

Mechanistic data come from a wide variety of studies and are generally not intended to identify a disease phenotype. This source of experimental data **includes in vitro and in vivo laboratory studies directed at identifying the cellular, biochemical, and molecular mechanisms that are related to chemicals that produces particular adverse effects**.

National Toxicology Program
U.S. Department of Health and Human Services


Human Animals
Indirect evidence?
Direct (surrogate ?)
Mechanism (in vitro) Modelling
Indirect evidence?
P
I
O
Direct
C
Judge indirectness

SCENARIO: Should oseltamivir be used for treatment of patients hospitalised with avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Hospitalised, clinical and serologically confirmed cases of avian influenza
Information sources:
Avian influenza data: Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: Le 2005, de Jong 2005, McKimm-Breschin 2003 and Hurt 2004.
Clinical trial data: trials for non-H5N1 influenza undertaken in the USA, China, Canada, Europe and Japan under pandemic conditions or seasonal outbreaks.

Outcome	Avian Influenza H5N1 Evidence			Seasonal Influenza Evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No of participants (No of trials)	Risk without treatment (Range)	Relative effect (95% CI)	Quality	Comments
Mortality		0.64 (33 to 100%)		0	-	-	-	No deaths reported in trials amongst healthy adults[1]
Duration of hospitalization (days)[2]	0	-	-	0	-	-	-	
Duration of disease (fever)[2]	0	-	-	2207[3] (5)	Median (3.89 to 6.0 days)[4]	-	⊕OOO[5] Very low	
Resistance	2	-	H5N1 was isolated from 2 patients in Viet Nam who died, who had been treated with oseltamivir. Viral isolates had an H274 neuraminidase base substitution which was associated with high level oseltamivir resistance in vitro. H274Y has also been shown to confer oseltamivir resistance in an animal model.	(2)		-	-	No evidence of widespread naturally-occurring resistance reported for non-H5N1 viruses.
Serious adverse effects[2]	0	-	-	0	-	-	-	
Cost of drugs per patient	0	-	-	0	-	-	-	

Footnotes:

1. In a single trial of healthy elderly participants, there was one death recorded in the placebo arm (n=91) with no deaths occurring in the treatment arm (n=77). No cause of death was given.
2. These data are indirect (i.e. for non-avian influenza) and thus only a proxy measure for what might be expected for avian influenza (H5N1).
3. This is the total number of participants for these 5 trials, confirmed from 3 sources, the ITT population was 1720. The ITTI population was 1404.
4. These data are based on 4 studies and the median time to resolution of symptoms.
5. Major uncertainty about the directness of the evidence, in addition there was significant inconsistency between the results of the studies.

H5N1 was isolated from 2 patients in Viet Nam who died, who had been treated with oseltamivir. Viral isolates had an H274 neuraminidase base substitution which was associated with high level oseltamivir resistance in vitro. H274Y has also been shown to confer oseltamivir resistance in an animal model.

One study has evaluated the effect of oseltamivir on neuraminidase and viral replication using H5N1 isolates from humans. Two additional studies using H5N1 isolated from ducks evaluated the effect of oseltamivir on viral replication (see annex 3). Consistent animal data from three studies in mice indicate that high-dose oseltamivir treatment increased survival in this animal model.

[2] A recent report of 8 cases (6 of these had complete data) described that 3 H5N1 patients who had cleared pharyngeal viral RNA by the end of 5 days treatment with oseltamivir survived. Three patients whose pharyngeal samples remained positive despite therapy died, two of whom had emergence of osletamivir-resistant variants (de Jong NEJM 2005).

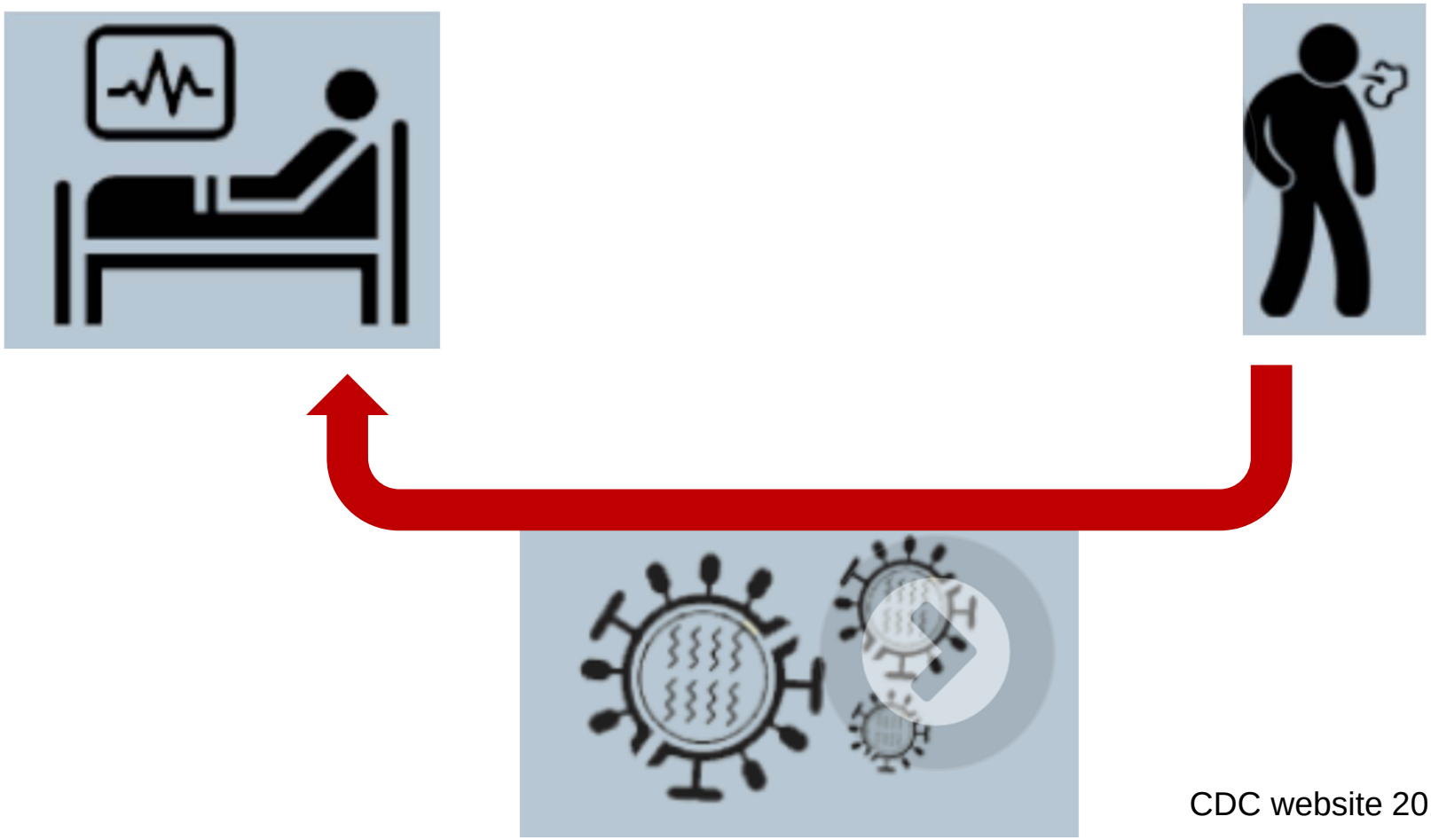
No evidence of resistance reported for H5N1. Viral isolates with the H274 neuraminidase base substitution which confers high level oseltamivir resistance are zanamivir sensitive in vitro.

There are very few studies describing animal and in vitro data about the effects of zanamivir on the H5N1 virus. Zanamivir is active in vitro and in vivo against oseltamivir-resistant H5N1 virus that contains the H274Y mutation (Le 2005).

Similar enough for treatment to have similar effects?

H5N1

H1N1 etc



CDC website 2019

Judgments

Similar virus: animal and in vitro data, characterization of the virus

- Population: Related, possibly same mechanism of action for neuraminidase inhibitor
- Outcomes: Resistance in animal models = humans

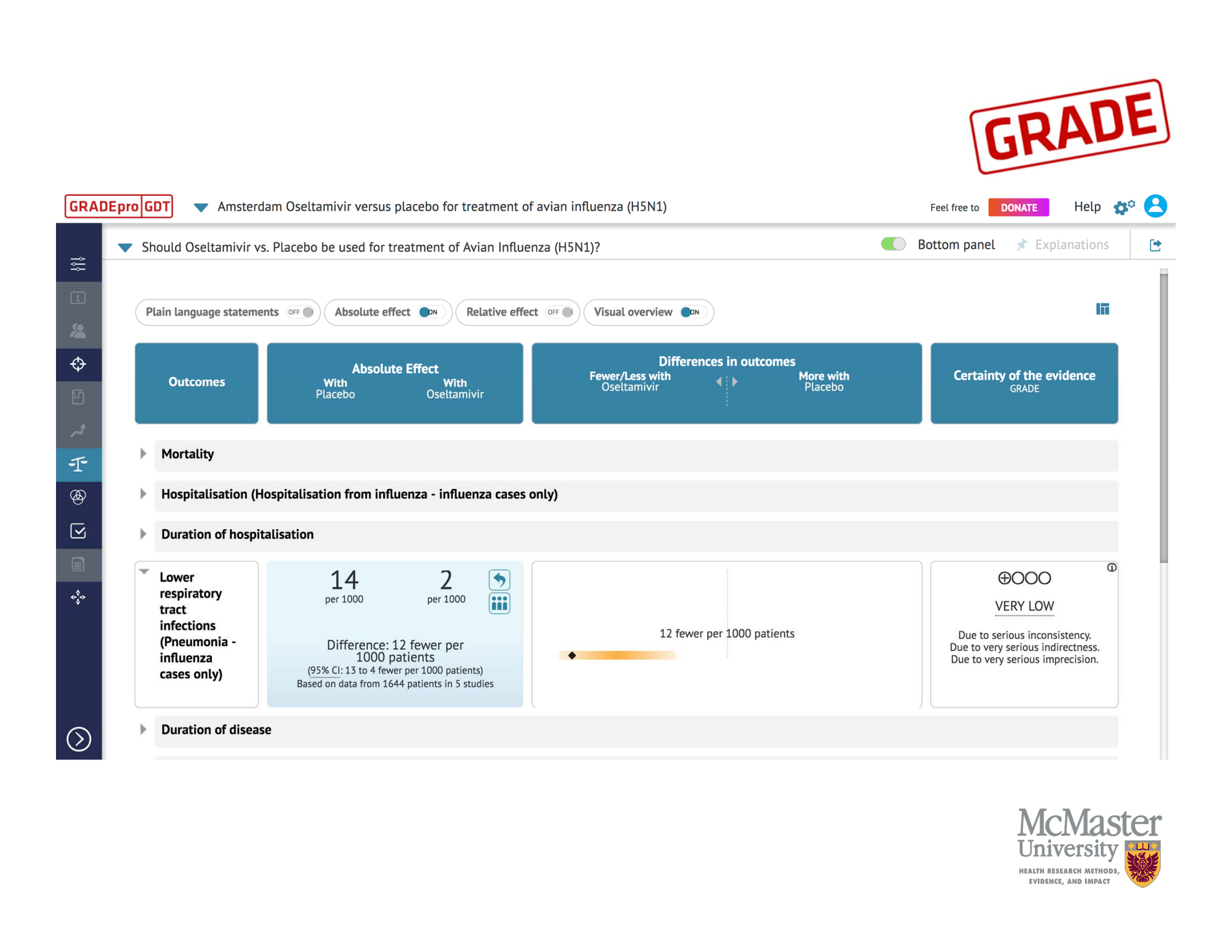
Mechanistic data helped to not dismiss the evidence from non-H5N1 studies

But: rated down for population indirectness because effects may be substantially different

Should Oseltamivir vs. Placebo be used for treatment of Avian Influenza (H5N1)? | Bottom panel | Explanations

Oseltamivir compared to Placebo for treatment of Avian Influenza (H5N1)

Certainty assessment							Summary of findings					
							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mortality												
0									not estimable		-	CRITICAL
Hospitalisation (Hospitalisation from influenza - influenza cases only)												
5	randomised trials	not serious	not serious	very serious [a]	very serious [b]	none			**RR 0.22** (0.02 to 2.16)	**0 fewer per 1,000** (from 2 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Duration of hospitalisation												
0									not estimable		-	CRITICAL
Lower respiratory tract infections (Pneumonia - influenza cases only)												
5	randomised trials	not serious	serious	very serious [a]	very serious [b]	none	2/982 (0.2%)	9/662 (1.4%)	**RR 0.15** (0.03 to 0.69)	**12 fewer per 1,000** (from 13 fewer to 4 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Duration of disease (assessed with: Time to alleviation of symptoms/median time to resolution of symptoms - influenza cases only)												
5 [c]	randomised trials	not serious	serious	very serious [a]	not serious	none			**HR 1.30** (1.13 to 1.50)	**1 fewer per 1,000** (from 2 fewer to 1 f	⨁◯◯◯ VERY LOW	IMPORTANT
Viral shedding (assessed with: Mean nasal titre of excreted virus at 24h)												
2	randomised trials	not serious	not serious	very serious [a]	very serious [b]	none			-	MD **0.73 days lower** (0.99 lower to 0.47 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Outbreak control												
0									not estimable		-	IMPORTANT
Resistance												
0									not estimable		-	CRITICAL
Serious adverse events (assessed with: Mention of significant or serious adverse effects)												
0									not estimable		-	CRITICAL
Minor adverse effects (assessed with: number and seriousness of adverse effects) [d]												
3 [e]	randomised trials	not serious	not serious	serious [f]	serious [b]	none			**OR --** (0.56 to 1.80)	**-- per 1,000** (from 2 fewer to 1 fewer)	⨁⨁◯◯ LOW	

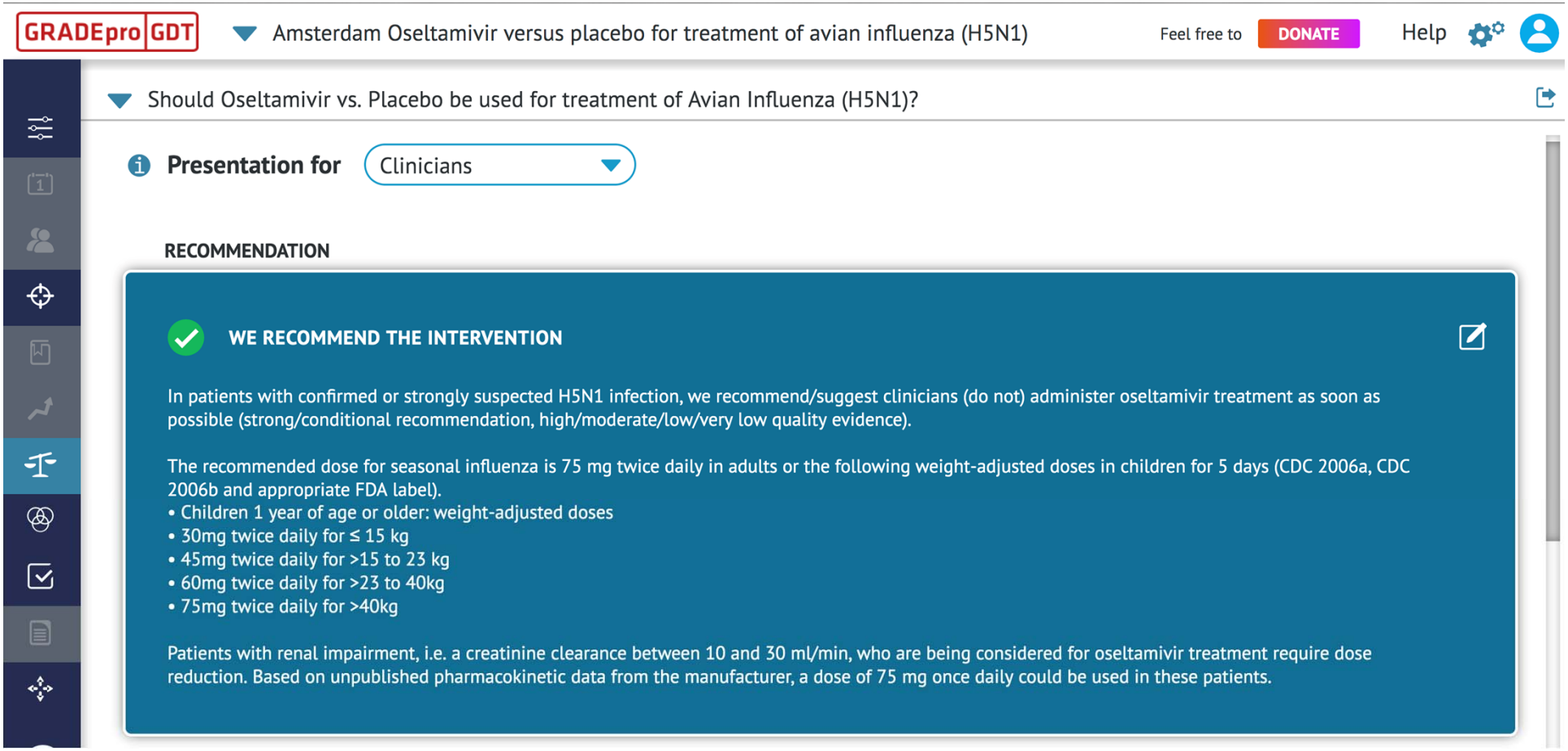


McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Should Oseltamivir vs. Placebo be used for treatment of Avian Influenza (H5N1)?

Bottom panel | Explanations

CRITERIA	SUMMARY OF JUDGEMENTS						IMPORTANCE FOR DECISION
PROBLEM	No	Probably no	Probably yes	**Yes**	Varies	Don't know	**HIGH**
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**	Varies	Don't know	**HIGH**
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial	Varies	Don't know	**LOW**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High	No included studies		**MODERATE**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			**HIGH**
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies / Don't know	**HIGH**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**	Varies	Don't know	**MODERATE**
FEASIBILITY	No	Probably no	Probably yes	**Yes**	Varies	Don't know	**MODERATE**



McMaster University

Michael G. DeGroote COCHRANE CANADA CENTRE

GRADE working group

Box 1. Key Steps in the Development of WHO Rapid Advice Guidelines

Decision about the topic and focus of the guidelines	**January 2006**
Decision about group composition and invitation of panel	
Formulation of questions and rating the importance of outcomes	
Literature search and preparation of evidence profiles	**February 17, 2006**
WHO panel co-chair met with systematic reviewers	
Panel chair and WHO panel co-chair corresponded electronically with systematic reviewers	
Review of evidence profiles and draft guidelines	
Panel chair met with WHO panel co-chair and systematic reviewers	
Panel meeting	**March 28–29, 2006**
Information about methods and agreement on procedures at the meeting	
Declaration of conflicts of interest	
Deliberation regarding the balance of benefits, harms, and costs for each question	
Agreement on recommendations, including the strength of recommendations, and research priorities	
Plans for updating the guidelines	
Agreement on final text of guidelines	**April 21, 2006**
Circulation of draft guidelines	
Approval by panel members	
Approval/publication by WHO	**May 19, 2006**

GRADE in Emergencies & Urgencies

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Preface

Using GRADE to respond to health questions with different levels of urgency

Kristina A. Thayer [a], Holger J. Schünemann [b,*]

[a] Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, P.O. Box 12233, Mail Drop K2-02, Research Triangle Park, NC 27709, USA

[b] Department of Clinical Epidemiology & Biostatistics, Department of Medicine, McMaster University, Health Sciences Centre, Room 2C14, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

ARTICLE INFO

Article history:
Received 15 March 2016
Received in revised form 21 March 2016
Accepted 21 March 2016
Available online xxxx

ABSTRACT

Increasing interest exists in applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health evidence. While ideally applied to evidence synthesized in systematic reviews and corresponding summary tables, such as evidence profiles, GRADE's correct application requires that "the evidence that was assessed and the methods that were used to identify and appraise that evidence should be clearly described." In this article, we suggest that GRADE could be applied to evidence assembled from narrative reviews, modelled (indirect) evidence, or evidence assembled as part of a rapid response, if the underlying judgments about the certainty in this evidence are based on the relevant GRADE domains and provid

Table 1
Examples of GRADE applied across different time scenarios.

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Example	West Virginia Elk River spill Population: community exposed to the chemical spill. Intervention/exposure: chemicals in the spill that contaminated water supply. Comparison: no chemicals in the spill. Outcomes: genotoxicity, developmental or reproductive toxicity, liver toxicity and others.	Melamine in composite food products Population: healthy people Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day. Comparison: higher than 0.5 mg/kg body weight of melamine from composition food. Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).	Avian influenza Population: people with suspected avian influenza infection. Intervention/exposure: oseltamivir. Comparison: no oseltamivir. Outcomes: mortality, duration of hospitalization, incidence of lower respiratory tract complications (used for this example of the certainty assessment below), antiviral drug resistance existing before treatment, and serious adverse events.	PFOA and birth weight Population: women of reproductive age and fetuses (before and/or during pregnancy or development). Intervention/exposure: perfluorooctanoic acid (PFOA; CAS# 335-67-1) or its salts. Comparison: lower levels of PFOA. Outcomes: fetal growth, birth weight, other measures of fetal or newborn size.
Type of evidence	Available evidence: animal toxicology studies in rodents for two chemicals in the spill (a 28-day study and a teratology study) and SAR analyses for other chemicals in the spill with no toxicology data.	Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.	Available evidence: five randomized trials in patients with seasonal flu (summarized in systematic reviews), case studies of patients with avian influenza, *in vitro* and *in vivo* animal data.	Available evidence: a systematic review of 18 non-randomized (observational) studies (10 were included in a meta-analysis).
GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments (note these are not necessarily reflecting judgments in the original scenarios).				
Risk of bias	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, pathologists blinded in their assessments or all animals accounted for). In this case it	Not serious	Serious based on some concern of risk of bias in the included studies (in the original report, the authors used an approach to rating certainty that accounted for risk of bias by lowering the certainty from high to

Table 1
Examples of GRADE applied across different time scenarios.

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Example	West Virginia Elk River spill Population: community exposed to the chemical spill. Intervention/exposure: chemicals in the spill that contaminated water supply. Comparison: no chemicals in the spill. Outcomes: genotoxicity, developmental or reproductive toxicity, liver toxicity and others.	Melamine in composite food products Population: healthy people Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day. Comparison: higher than 0.5 mg/kg body weight of melamine from composition food. Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).	Avian influenza Population: people with suspected avian influenza infection. Intervention/exposure: oseltamivir. Comparison: no oseltamivir. Outcomes: mortality, duration of hospitalization, incidence of lower respiratory tract complications (used for certainty antiviral before tr adverse e	PFOA and birth weight Population: women of reproductive age and fetuses (before and/or during pregnancy or development). Intervention/exposure: perfluorooctanoic acid (PFOA; CAS# 335-67-1) or its salts. Comparison: lower levels of PFOA. l or
Type of evidence	Available evidence: animal toxicology studies in rodents for two chemicals in the spill (a 28-day study and a teratology study) and SAR analyses for other chemicals in the spill with no toxicology data.	Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.	Available trials in p (summar reviews), with avia *in vivo* ar	tic ere
GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judg				*he original scenarios).*
Risk of bias	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, pathologists blinded in their assessments or all animals accounted for). In this case it	Not serio	n of dies hors rtainty by igh to

Rest of table summarizes:

- GRADE domains
  - risk of bias, imprecision, indirectness, inconsistency, publication bias, magnitude, etc.
- Certainty in evidence
- Possible summary statements

Summary

Focused on highest certainty evidence

Used animal evidence and mechanistic evidence to inform judgments about indirectness

- Dismiss or rate down?
- Integrated in indirectness judgment

Rapidly done, recommendation developed

GRADE

McMaster University

HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Justification for the recommendation

This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance and costs of treatment. Despite the lack of controlled treatment data for H5N1, this is a strong recommendation, in part, because there is a lack of known effective alternative pharmacological interventions at this time.

GRADE in urgencies

Organizations in environmental health and other areas looking for structured frameworks for evidence synthesis

- "Fit for purpose" – sometimes systematic review not possible to assemble evidence, i.e., need for emergency response
- GRADE's certainty in the evidence

Environment International 92–93 (2016) 585–589

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Preface

Using GRADE to respond to health questions with different levels of urgency

Kristina A. Thayer [a], Holger J. Schünemann [b,*]

[a] Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, P.O. Box 12233, Mail Drop K2-02, Research Triangle Park, NC 27709, USA
[b] Department of Clinical Epidemiology & Biostatistics, Department of Medicine, McMaster University, Health Sciences Centre, Room 2C14, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

Urgent response: one to two weeks

Melamine in composite food products
Population: healthy people
Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day.
Comparison: higher than 0.5 mg/kg body weight of melamine from composition food.
Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).
Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.

GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments (note these are not necessarily reflecting judgments in the original scenarios).

Risk of bias	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals were accounted for). Ideally, RoB assessments would be available for individual studies and summarized across studies. In the Elk River example, the number of animal studies was small and could be assessed at the individual level within a short-time frame. A de novo risk of bias evaluation may not be feasible in cases where evidence is drawn from existing narrative risk assessments that summarize a large body of literature. Nevertheless, it may still be possible to assess risk of bias based on the uncertainties and evidence limitations described in the risk assessment. SAR: could be assessed using OECD model validation or similar guidance that recommends presentation of a defined domain of applicability for a defined endpoint supported by appropriate measures of goodness-of-fit (OECD, 2007).	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, pathologists blinded in their assessments or all animals accounted for). In this case it appears that the animal studies did not report that it was randomized and, thus, may be at risk of bias.	Not serious	Serious based on some concern of risk of bias in the included studies (in the original report, the authors used an approach to rating certainty that accounted for risk of bias by lowering the certainty from high to moderate).
Imprecision	Could be assessed for both animal data and SAR (e.g., considering statistical or numerical uncertainty in model parameters).	While no summary estimates are available, an assessment could be guided by the availability of data from only 100 animals in different exposure groups which would result in wide confidence intervals.	Serious	Not serious
Inconsistency	Could be assessed for both animal data and SAR (e.g., assessing similarity of results based on applying different models).	Only one study was included and therefore no inconsistency is present (Guyatt et al., 2011d).	Not serious	Not serious

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Indirectness	Animal studies: could be assessed using GRADE's indirectness assessment (Guyatt et al., 2011c; Schünemann et al., 2013). Animal studies may be rated down for indirectness if concerns exist about extrapolating from animals to humans, e.g., relevance of animal model for the health outcome of interest or route of exposure. SAR: could be assessed based on evidence of direct relation of the model to a defined endpoint. SAR would typically be downgraded for indirectness.	This could be rated down for serious indirectness of extrapolating from animals to humans and uncertainty about the levels of exposure (different levels or routes of exposure evaluated than those one is interested in and modeling of exposure levels based on composition food products from more exact exposures fed to animals). Further concerns would likely be described for the comparator.	Very serious	Not serious

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Indirectness	Animal studies: could be assessed using GRADE's indirectness assessment (Guyatt et al., 2011c; Schünemann et al., 2013). Animal studies may be rated down for indirectness if concerns exist about extrapolating from animals to humans, e.g., relevance of animal model for the health outcome of interest or route of exposure. SAR: could be assessed based on evidence of direct relation of the model to a defined endpoint. SAR would typically be downgraded for indirectness.	This could be rated down for serious indirectness of extrapolating from animals to humans and uncertainty about the levels of exposure (different levels or routes of exposure evaluated than those one is interested in and modeling of exposure levels based on composition food products from more exact exposures fed to animals). Further concerns would likely be described for the comparator.	Very serious	Not serious
Possible summary statement*	There is low certainty in the evidence suggesting no association between the exposure and toxicity based on SAR analyses.	There is very low certainty in the evidence suggesting no association between levels of melamine exposure from composition food products below 0.5 mg/kg body weight per day and urinary tumors.	There is very low certainty suggesting that oseltamivir reduces hospitalization in patients with avian influenza.	There is moderate certainty in the evidence suggesting that PFOA is associated with harmful effects on fetal growth.

* Note, this hypothetical summary was derived by the authors of this editorial, not those of the original report.

Today

- GRADE “very” brief background
- When and how to integrate
- Human, animal, “mechanistic” evidence

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Anatomy of a guideline

WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetali Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjdaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections with H5N1 virus worldwide. Despite international agreement to stockpile antivirals, evidence-based guidelines for their use do not exist. WHO assembled an international multidisciplinary panel to develop rapid advice for the pharmacological management of human H5N1 virus infection in the current pandemic alert period. A transparent

Lancet Infect Dis 2007; 7: 21–31

Italian National Cancer Institute Regina Elena, INFORMA Unit, Department of

A World Health Organization guideline

WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetali Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjdaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections *Lancet Infect Dis* 2007; 7: 21–31

Schunemann, Hill et al., The Lancet ID & PLOS Med, 2007

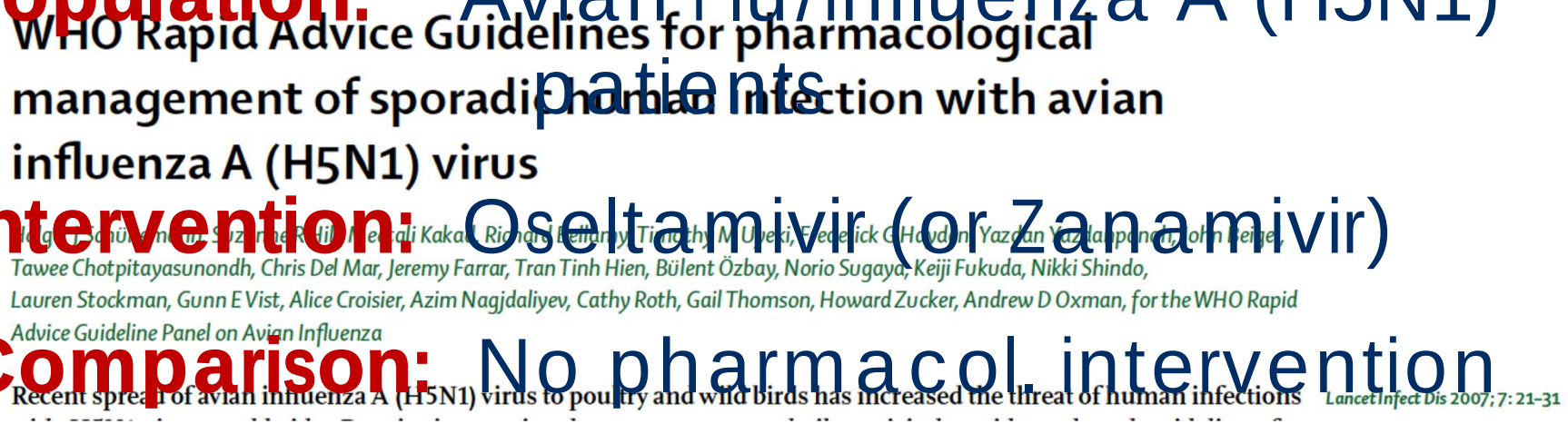
A World Health Organization guideline

Population: Avian Flu/influenza A (H5N1) patients

Intervention: Oseltamivir (or Zanamivir)

Comparison: No pharmacol. intervention

Outcomes: Mortality, hospitalizations, resources, adverse outcomes, antimicrobial resistance


WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjdaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections

Lancet Infect Dis 2007; 7: 21–31

Schunemann, Hill et al., The Lancet ID & PLOS Med, 2007

Oseltamivir for Avian Flu

Summary of findings:

No clinical trial of oseltamivir for treatment of H5N1 patients.

4 systematic reviews and health technology assessments (HTA) reporting on 5 studies of oseltamivir in seasonal influenza.

- Hospitalization: OR 0.22 (0.02 – 2.16)
- Pneumonia: OR 0.15 (0.03 - 0.69)

3 published case series.

Many in vitro and animal studies.

No alternative that was more promising at present. No important side effects.

Cost: 40 Euro per treatment course


GRADE

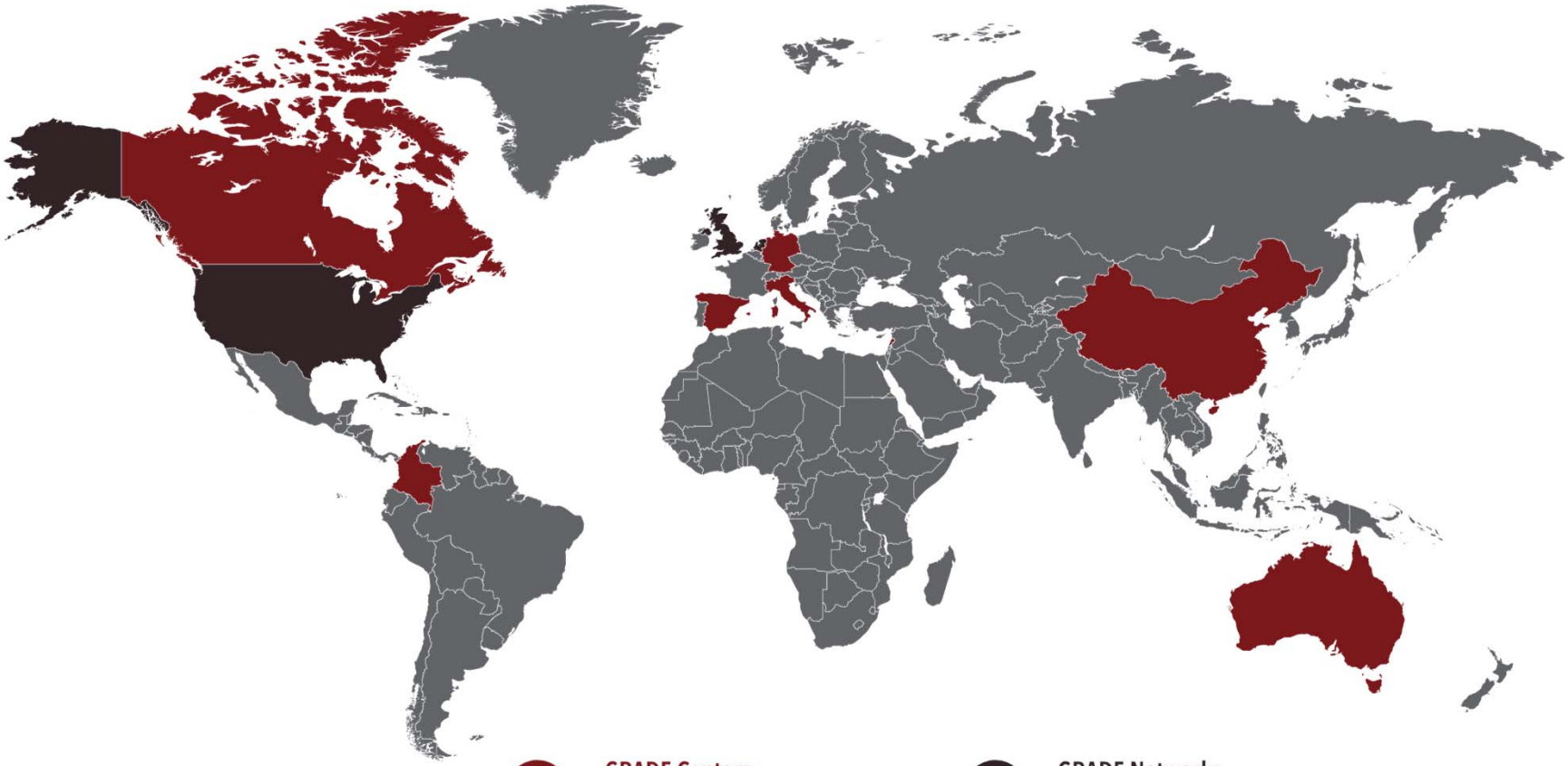
GRADE working group

After over 20 years of increasing confusion, beginning in 2000, GRADE developed a **unifying, transparent and sensible system for grading the certainty of evidence and making decisions**

- WHO, NICE, CADTH, CDC, AHRQ, professional societies, academic institutions since 2000 – over 100 use GRADE
- Evidence synthesis (systematic reviews, HTA) and guidelines
- International & diverse contributors (>600)
- 2008/16 BMJ series; 2011 -? JCE/EHI series – over 40,000 cites
- Various other publications (incl. GRADE Handbook)
- IT applications GRADEpro | GDT

CMAJ 2003, BMJ 2004, BMC 2004, BMC 2005, AJRCCM 2006, Chest 2006, BMJ 2008, JCE 2011-2018, EHI 2017 -

GRADE



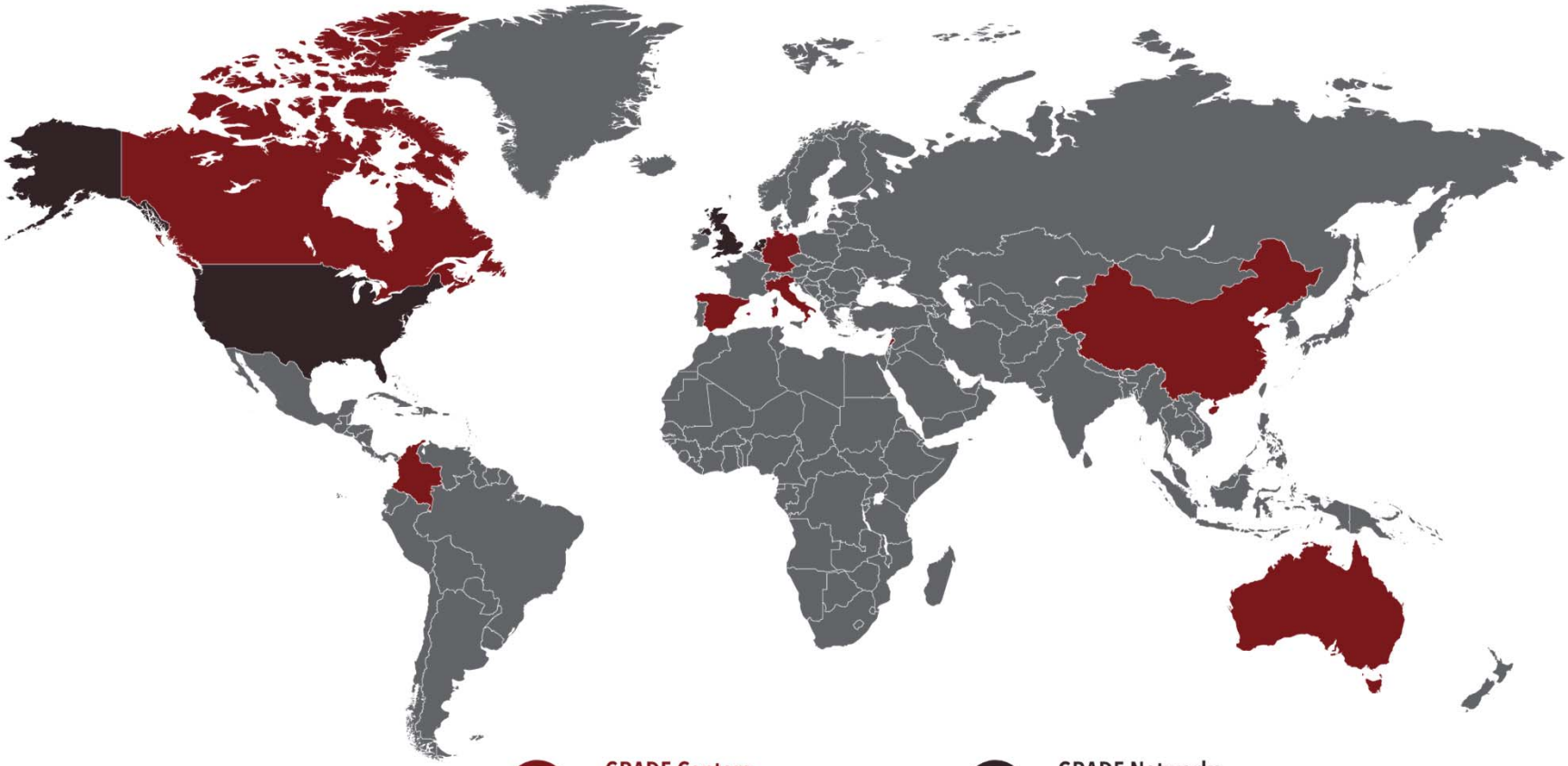
GRADE Centers

McMaster University GRADE Center, **Canada**
Lanzhou University GRADE Center, **China**
Barcelona GRADE Center, **Spain**
Freiburg University GRADE Center, **Germany**
American University of Beirut GRADE Center, **Lebanon**
Lazio Region-ASL Rome GRADE Center, **Italy**
Javeriana Bogota GRADE Center, **Colombia**
JBI Adelaide GRADE Center, **Australia**

GRADE Networks

U.S. GRADE Network, **United States**
Dutch GRADE Network, **Netherlands**
UK GRADE Network, **United Kingdom**

GRADE



Approved: South Africa, , Czech Rep.,
Planned: Japan, Poland, Brazil

GRADE Centers

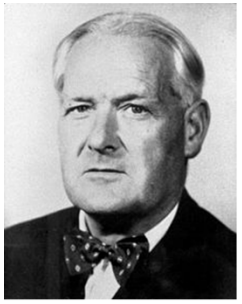
McMaster University GRADE Center, **Canada**
Lanzhou University GRADE Center, **China**
Barcelona GRADE Center, **Spain**
Freiburg University GRADE Center, **Germany**
American University of Beirut GRADE Center, **Lebanon**
Lazio Region-ASL Rome GRADE Center, **Italy**
Javeriana Bogota GRADE Center, **Colombia**
JBI Adelaide GRADE Center, **Australia**

GRADE Networks

U.S. GRADE Network, **United States**
Dutch GRADE Network, **Netherlands**
UK GRADE Network, **United Kingdom**

Over 100 organisations

GRADE came from epidemiology



Certainty in causation

Meeting January 14 1965

President's Address

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

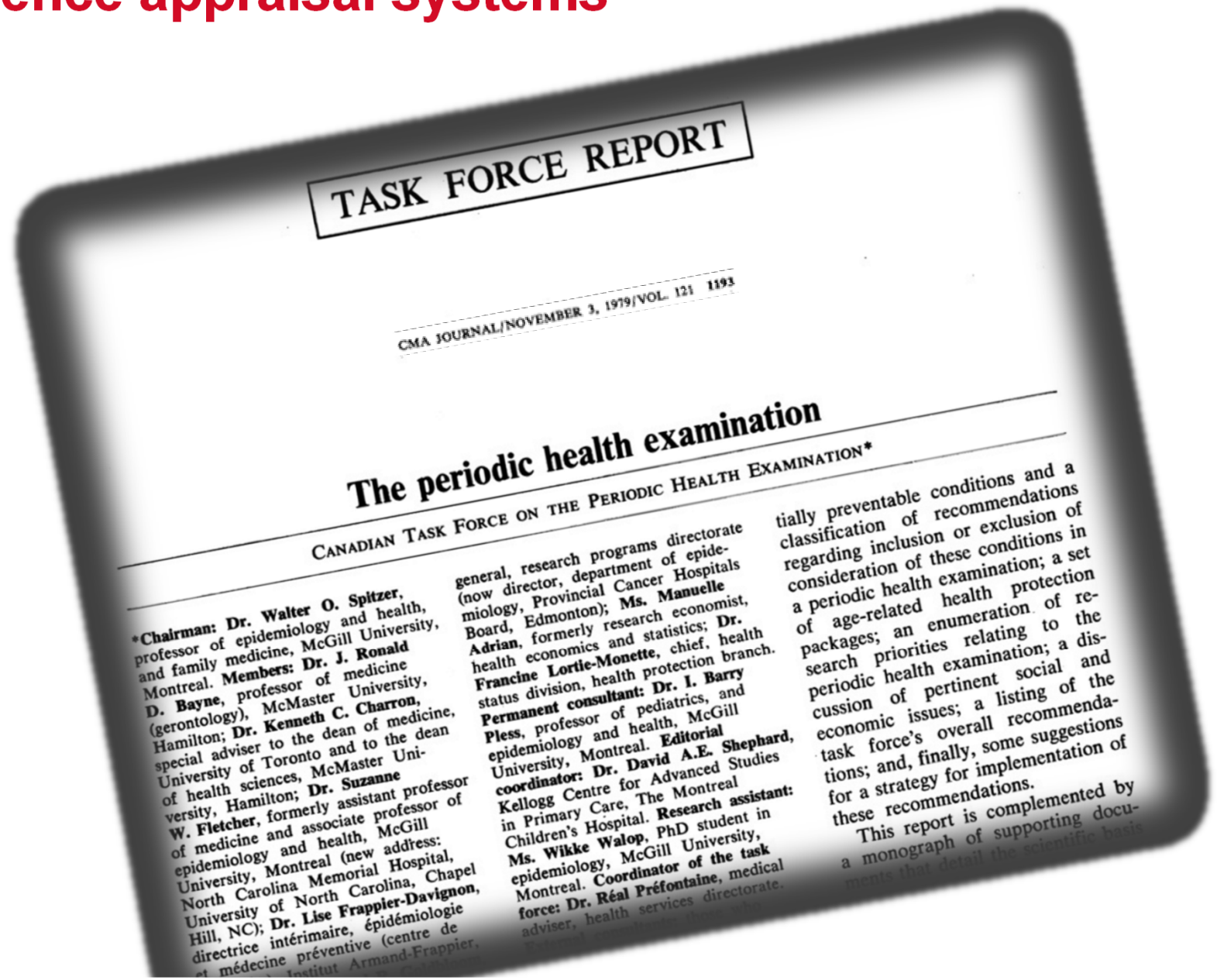
At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to our own. How in the first place do we detect these relationships between sickness, injury and conditions of work? How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized? Upon what basis should we proceed to pass from observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) *Strength*. First upon my list I would put the strength of the association. To take a very old

Recommendations & the origin of evidence appraisal systems



TASK FORCE REPORT

CMA JOURNAL/NOVEMBER 3, 1979/VOL. 121 1193

The periodic health examination

CANADIAN TASK FORCE ON THE PERIODIC HEALTH EXAMINATION*

*Chairman: Dr. Walter O. Spitzer, professor of epidemiology and health, and family medicine, McGill University, Montreal. Members: Dr. J. Ronald D. Bayne, professor of medicine (gerontology), McMaster University, Hamilton; Dr. Kenneth C. Charron, special adviser to the dean of medicine, University of Toronto and to the dean of health sciences, McMaster University, Hamilton; Dr. Suzanne W. Fletcher, formerly assistant professor of medicine and associate professor of epidemiology and health, McGill University, Montreal (new address: North Carolina Memorial Hospital, University of North Carolina, Chapel Hill, NC); Dr. Lise Frappier-Davignon, directrice intérimaire, épidémiologie et médecine préventive (centre de l'Institut Armand-Frappier, general, research programs directorate (now director, department of epidemiology, Provincial Cancer Hospitals Board, Edmonton); Ms. Manuelle Adrian, formerly research economist, health economics and statistics; Dr. Francine Lortie-Monette, chief, health status division, health protection branch. Permanent consultant: Dr. I. Barry Pless, professor of pediatrics, and epidemiology and health, McGill University, Montreal. Editorial coordinator: Dr. David A.E. Shephard, Kellogg Centre for Advanced Studies in Primary Care, The Montreal Children's Hospital. Research assistant: Ms. Wikke Walop, PhD student in epidemiology, McGill University, Montreal. Coordinator of the task force: Dr. Réal Préfontaine, medical adviser, health services directorate.

tially preventable conditions and a classification of recommendations regarding inclusion or exclusion of consideration of these conditions in a periodic health examination; a set of age-related health protection packages; an enumeration of research priorities relating to the periodic health examination; a discussion of pertinent social and economic issues; a listing of the task force's overall recommendations; and, finally, some suggestions for a strategy for implementation of these recommendations.

This report is complemented by a monograph of supporting documents that detail the scientific basis

Effectiveness of intervention

The effectiveness of intervention was graded according to the quality of the evidence obtained, as follows:

I: Evidence obtained from at least one properly randomized controlled trial.

II-1: Evidence obtained from well designed cohort or case–control analytic studies, preferably from more than one centre or research group.

II-2: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

ORCE REPORT

NAL/NOVEMBER 3, 1979/VOL. 121 1193

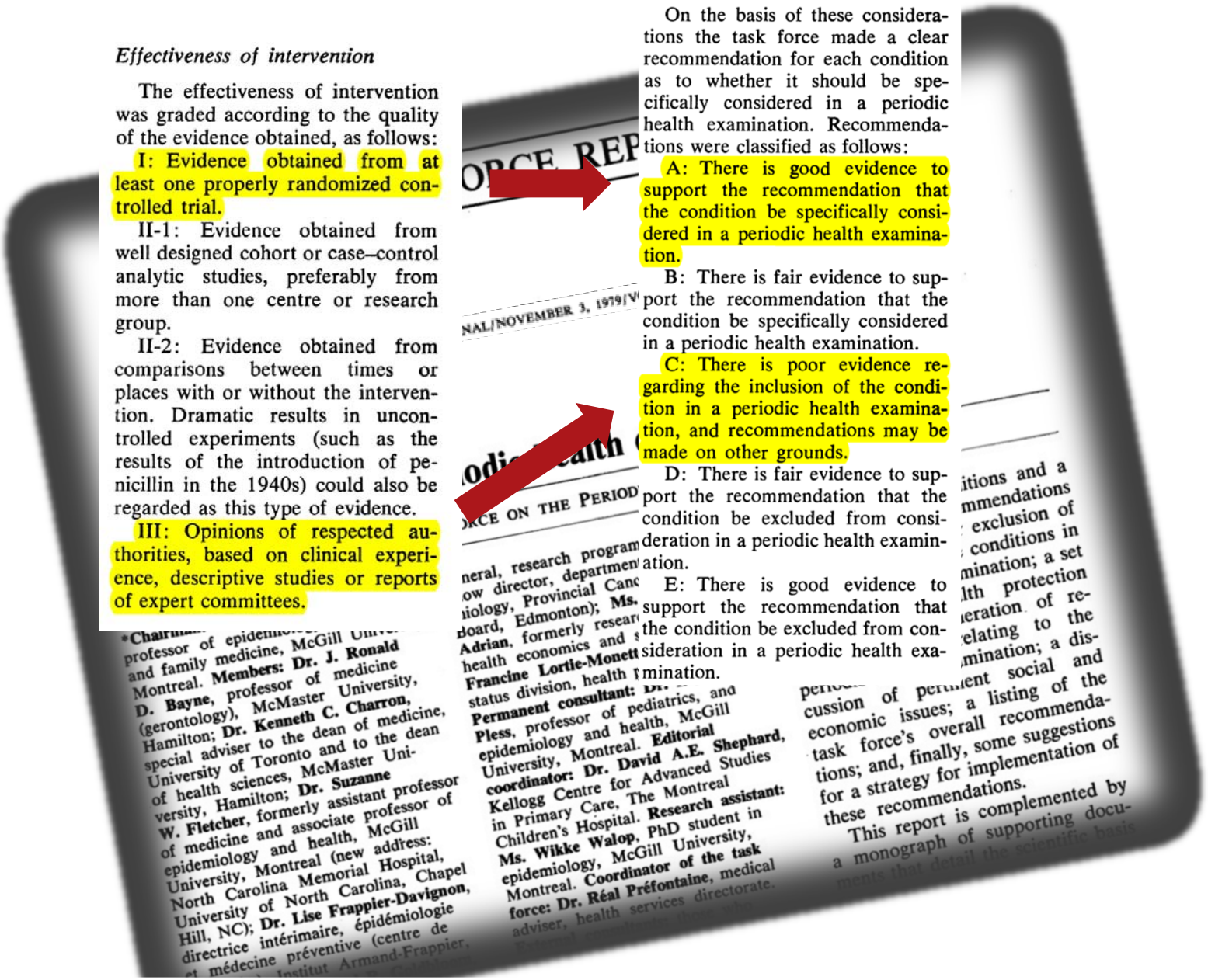
odic health examination

ORCE ON THE PERIODIC HEALTH EXAMINATION*

professor of epidemiol... and family medicine, McGill Univ... Montreal. **Members: Dr. J. Ronald D. Bayne**, professor of medicine (gerontology), McMaster University, Hamilton; **Dr. Kenneth C. Charron**, special adviser to the dean of medicine, University of Toronto and to the dean of health sciences, McMaster University, Hamilton; **Dr. Suzanne W. Fletcher**, formerly assistant professor of medicine and associate professor of epidemiology and health, McGill University, Montreal (new address: North Carolina Memorial Hospital, University of North Carolina, Chapel Hill, NC); **Dr. Lise Frappier-Davignon**, directrice intérimaire, épidémiologie et médecine préventive (centre de ... Institut Armand-Frappier, ...neral, research programs directorate ...ow director, department of epide... ...iology, Provincial Cancer Hospitals ...board, Edmonton); **Ms. Manuelle Adrian**, formerly research economist, health economics and statistics; **Dr. Francine Lortie-Monette**, chief, health status division, health protection branch. **Permanent consultant: Dr. I. Barry Pless**, professor of pediatrics, and epidemiology and health, McGill University, Montreal. **Editorial coordinator: Dr. David A.E. Shephard**, Kellogg Centre for Advanced Studies in Primary Care, The Montreal Children's Hospital. **Research assistant: Ms. Wikke Walop**, PhD student in epidemiology, McGill University, Montreal. **Coordinator of the task force: Dr. Réal Préfontaine**, medical adviser, health services directorate. ...

tially preventable conditions and a classification of recommendations regarding inclusion or exclusion of consideration of these conditions in a periodic health examination; a set of age-related health protection packages; an enumeration of research priorities relating to the periodic health examination; a discussion of pertinent social and economic issues; a listing of the task force's overall recommendations; and, finally, some suggestions for a strategy for implementation of these recommendations.

This report is complemented by a monograph of supporting documents that detail the scientific basis



Effectiveness of intervention

The effectiveness of intervention was graded according to the quality of the evidence obtained, as follows:

I: Evidence obtained from at least one properly randomized controlled trial.

II-1: Evidence obtained from well designed cohort or case–control analytic studies, preferably from more than one centre or research group.

II-2: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Classification of recommendations

On the basis of these considerations the task force made a clear recommendation for each condition as to whether it should be specifically considered in a periodic health examination. Recommendations were classified as follows:

A: There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.

B: There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.

C: There is poor evidence regarding the inclusion of the condition in a periodic health examination, and recommendations may be made on other grounds.

D: There is fair evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

E: There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

GRADE came from epidemiology

Etiology

PECO

Association vs. Causation

A sensible question

Population: People

Exposures: Ethylene Oxide
Comparison: no, different levels of, exact cut offs of Ethylene Oxide

Outcomes: different types of cancer

PECO

Decisions

Population: People

Intervention: Regulation to ban/reduce to certain level

Comparison: no regulation

Outcomes: cancer, road safety (ethylene glycol), surgical infections

PICO

Confidence in estimates of effect

100% confident →

0% confident →

Schünemann et al. JECH 2010

Confidence in estimates of effect

100% confident →

0% confident →

← starting point?

Schünemann et al. JECH 2010

Confidence in estimates of effect

100% confident →

0% confident →

← starting point?

<u>Bradford Hill Criteria</u>

Strength
Consistency
Temporality
Biological gradient
Specificity
Biological Plausibility
Coherence
Experiment
Analogy

Schünemann et al. JECH 2010

Confidence in estimates of effect

100% confident →

0% confident →

← starting point?

<u>Bradford Hill Criteria</u>

Strength
Consistency
Temporality
Biological gradient
Specificity
Biological Plausibility
Coherence
Experiment
Analogy

Good, but insufficient (publication bias?)

Schünemann et al. JECH 2010

Why did GRADE not use Bradford Hill Characteristics

- Not complete
- Not operationalized
  - Random error
  - Experimental design
  - Consistency
  - Biological plausibility, etc
- Not completely thought through
  - Association
  - Intervention
  - Prognosis
  - Tests, etc
- Not fit for what follows from an exposure assessment – policy & interventions

Confidence in estimates of effect or causality

100% confident →

0% confident →

Moderate

Low

Very low

Schünemann et al. JECH 2010

Confidence in estimates of effect or causality

100% confident →

0% confident →

← GRADE's starting point

High

Moderate

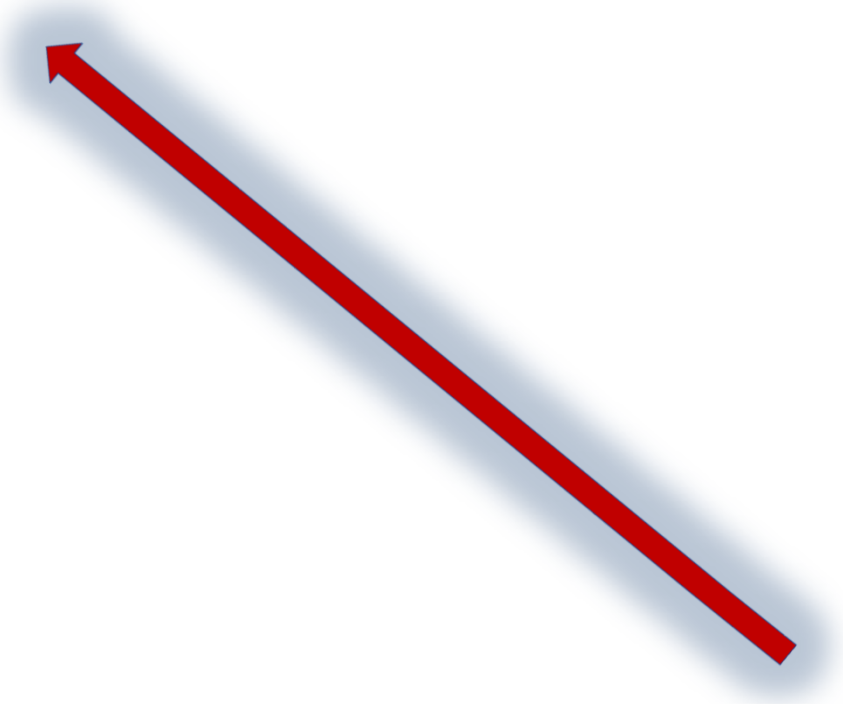
Low

Very low

Schünemann et al. JECH 2010

GRADE considers Bradford Hill

Bradford Hill



GRADE

Table 1 Bradford Hill criteria of causality and their relation to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for upgrading and downgrading

Bradford Hill criteria	Consideration in GRADE
Strength	Strength of association and imprecision in effect estimate
Consistency	Consistency across studies, ie, across different situations (different researchers)
Temporality	Study design, specific study limitations; RCTs fulfil this criterion better than observational studies, properly designed and conducted observational studies
Biological gradient	Dose—response gradient
Specificity	Indirectness
Biological plausibility	Indirectness
Coherence	Indirectness
Experiment	Study design, randomisation, properly designed and conducted observational studies
Analogy	Existing association for critical outcomes will lead to not downgrading the quality, indirectness

Schünemann et al. JECH 2010

Causality considerations

GRADE

Not everything made sense

50 years later

Bradford Hill – one person

Spitzer, Sackett et al – few people

GRADE – community of more than 600

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Certainty of evidence

How confident in the research?

Are the research studies well done? Risk of bias

Are the results consistent across studies ? Inconsistency

How directly do the results relate to our question? Indirectness

Is the effect size precise - due to random error? Imprecision

Are these all of the studies that have been conducted? Pub Bias

Is there anything else that makes us particularly certain? Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Operationalization

GRADE

Risk of bias?

Are the results consistent across studies ? Inconsistency

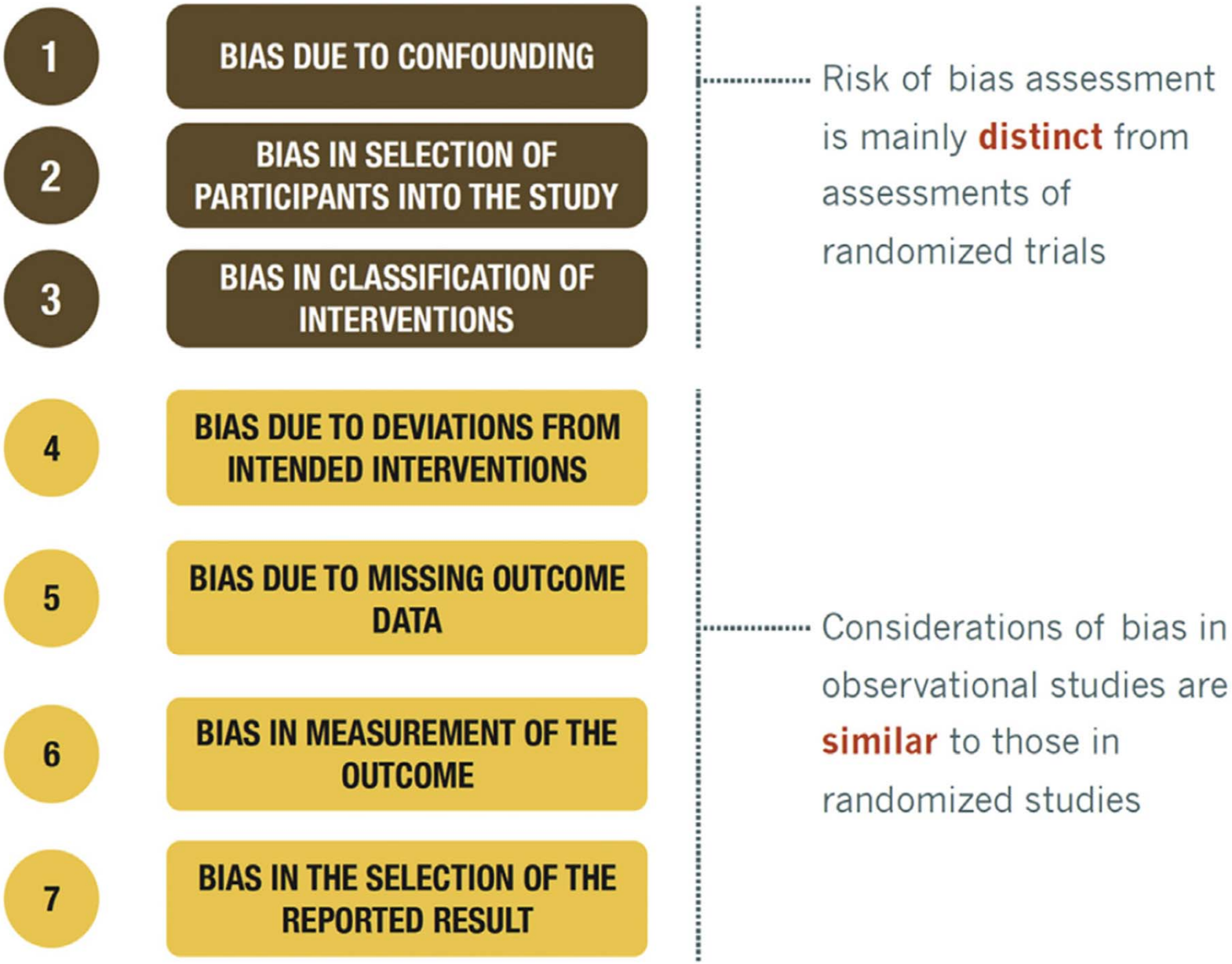
How directly do the results relate to our question? Indirectness

Is the effect size precise - due to random error? Imprecision

Are these all of the studies that have been conducted? Pub. Bias

Is there anything else that makes us particularly certain? Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT


1
BIAS DUE TO CONFOUNDING
2
BIAS IN SELECTION OF PARTICIPANTS INTO THE STUDY
3
BIAS IN CLASSIFICATION OF INTERVENTIONS
Risk of bias assessment is mainly distinct from assessments of randomized trials
4
BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS
5
BIAS DUE TO MISSING OUTCOME DATA
6
BIAS IN MEASUREMENT OF THE OUTCOME
7
BIAS IN THE SELECTION OF THE REPORTED RESULT
Considerations of bias in observational studies are similar to those in randomized studies

GRADE

GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias)

GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence

A risk of bias instrument for non-randomized studies of exposures: A users' guide to its application in the context of GRADE

Evaluation of the risk of bias in non-randomized studies of interventions (ROBINS-I) and the 'target experiment' concept in studies of exposures: Rationale and preliminary instrument development

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Operationalization

GRADE guidelines: 7. Rating the quality of evidence—inconsistency

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Operationalization

Are the results consistent across studies ? Inconsistency

Can inconsistency be explained? – PECO items, explore

Overlapping confidence intervals

Similarity of the point estimates

I^2

Test for heterogeneity

GRADE guidelines: 7. Rating the quality of evidence—inconsistency

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Operationalization

GRADE

Is the effect size precise - due to random error?
Imprecision

Are these all of the studies that have been conducted?
Pub. Bias

Is there anything else that makes us particularly certain?
Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Indirectness – evidence integration

GRADE

How directly do the results relate to the question of interest? Indirectness

RESEARCH ARTICLE

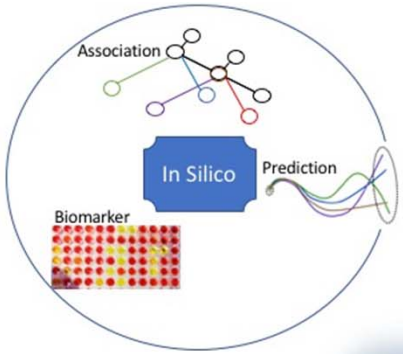
Facilitating healthcare decisions by assessing the certainty in the evidence from preclinical animal studies

Carlijn R. Hooijmans[1], Rob B. M. de Vries[1], Merel Ritskes-Hoitinga[1], Maroeska M. Rovers[1], Mariska M. Leeflang[2], Joanna IntHout[1], Kimberley E. Wever[1], Lotty Hooft[3], Hans de Beer[4], Ton Kuijpers[5], Malcolm R. Macleod[6], Emily S. Sena[6], Gerben ter Riet[7], Rebecca L. Morgan[8,9], Kristina A. Thayer[10], Andrew A. Rooney[10], Gordon H. Guyatt[8,9], Holger J. Schünemann[8,9], Miranda W. Langendam[2]*, on behalf of the GRADE Working Group[¶]

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Whatever the question

The population of interest is in humans



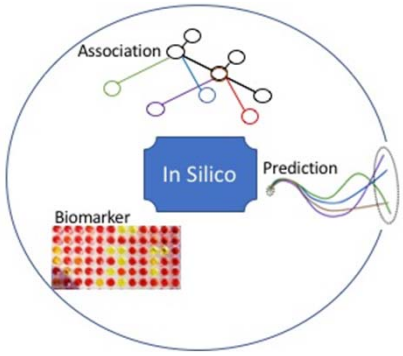
Mechanistic data

Mechanistic data come from a wide variety of studies and are generally not intended to identify a disease phenotype. This source of experimental data **includes in vitro and in vivo laboratory studies directed at identifying the cellular, biochemical, and molecular mechanisms that are related to chemicals that produces particular adverse effects**.

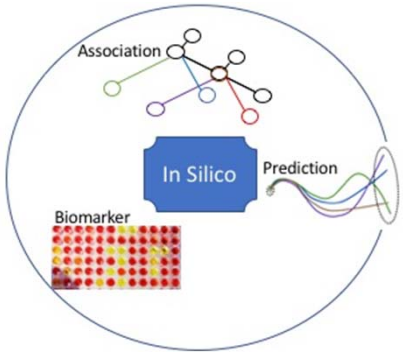
Another broad class of mechanistic data relates to the toxicokinetics of a chemical (NRC 2014a).

National Toxicology Program
U.S. Department of Health and Human Services

Indirectness is a continuum



Indirectness is a continuum



Animal studies

- Considered a different species
- Typically indirect, but
- First guidance from WHO in which evidence is considered moderate on the basis of a single study in animals

GRADE

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

Indirectness affects all domains

P

E

C

O

Outcome: Cancer

Domain (original question asked	Description	Judgment - Is the evidence sufficiently direct?
Population:		○ Yes ○ Probably yes ○ Probably no ○ No
Intervention: exposure		○ Yes ○ Probably yes ○ Probably no ○ No
Comparator: [comparison]		○ Yes ○ Probably yes ○ Probably no ○ No
Direct comparison		○ Yes ○ Probably yes ○ Probably no ○ No
Outcome: Cancer		○ Yes ○ Probably yes ○ Probably no ○ No
Final judgment about indirectness across domains:	○ No indirectness ○ Serious indirectness ○ Very serious indirectness	

Cancel Apply

Indirectness affects all domains

P

E

C

O

Outcome: Cancer

Domain (original question asked	Description	Judgment - Is the evidence sufficiently direct?
Population:		○ Yes ○ Probably yes ○ Probably no ○ No
Intervention: exposure		○ Yes ○ Probably yes ○ Probably no ○ No
Comparator: [comparison]		○ Yes ○ Probably yes ○ Probably no ○ No
Direct comparison		○ Yes ○ Probably yes ○ Probably no ○ No
Outcome: Cancer		○ Yes ○ Probably yes ○ Probably no ○ No
Final judgment about indirectness across domains:	○ No indirectness ○ Serious indirectness ○ Very serious indirectness	

Cancel | Apply

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Preface

Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes

Rebecca L. Morgan[a], Paul Whaley[b], Kristina A. Thayer[c], Holger J. Schünemann[a,d,*]

Indirectness affects all domains

P

E

C

O

Outcome: Cancer

Domain (original question asked	Description	Judgment - Is the evidence sufficiently direct?
Population:		○ Yes ○ Probably yes ○ Probably no ○ No
Intervention: exposure		○ Yes ○ Probably yes ○ Probably no ○ No
Comparator: [comparison]		○ Yes ○ Probably yes ○ Probably no ○ No
Direct comparison		○ Yes ○ Probably yes ○ Probably no ○ No
Outcome: Cancer		○ Yes ○ Probably yes ○ Probably no ○ No
Final judgment about indirectness across domains:	○ No indirectness ○ Serious indirectness ○ Very serious indirectness	

Cancel | Apply

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

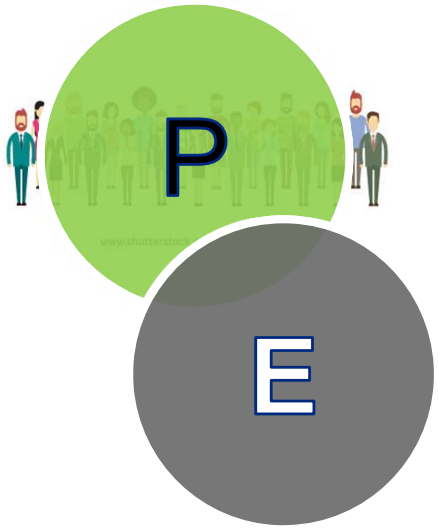
Preface

Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes

Rebecca L. Morgan[a], Paul Whaley[b], Kristina A. Thayer[c], Holger J. Schünemann[a,d,*]

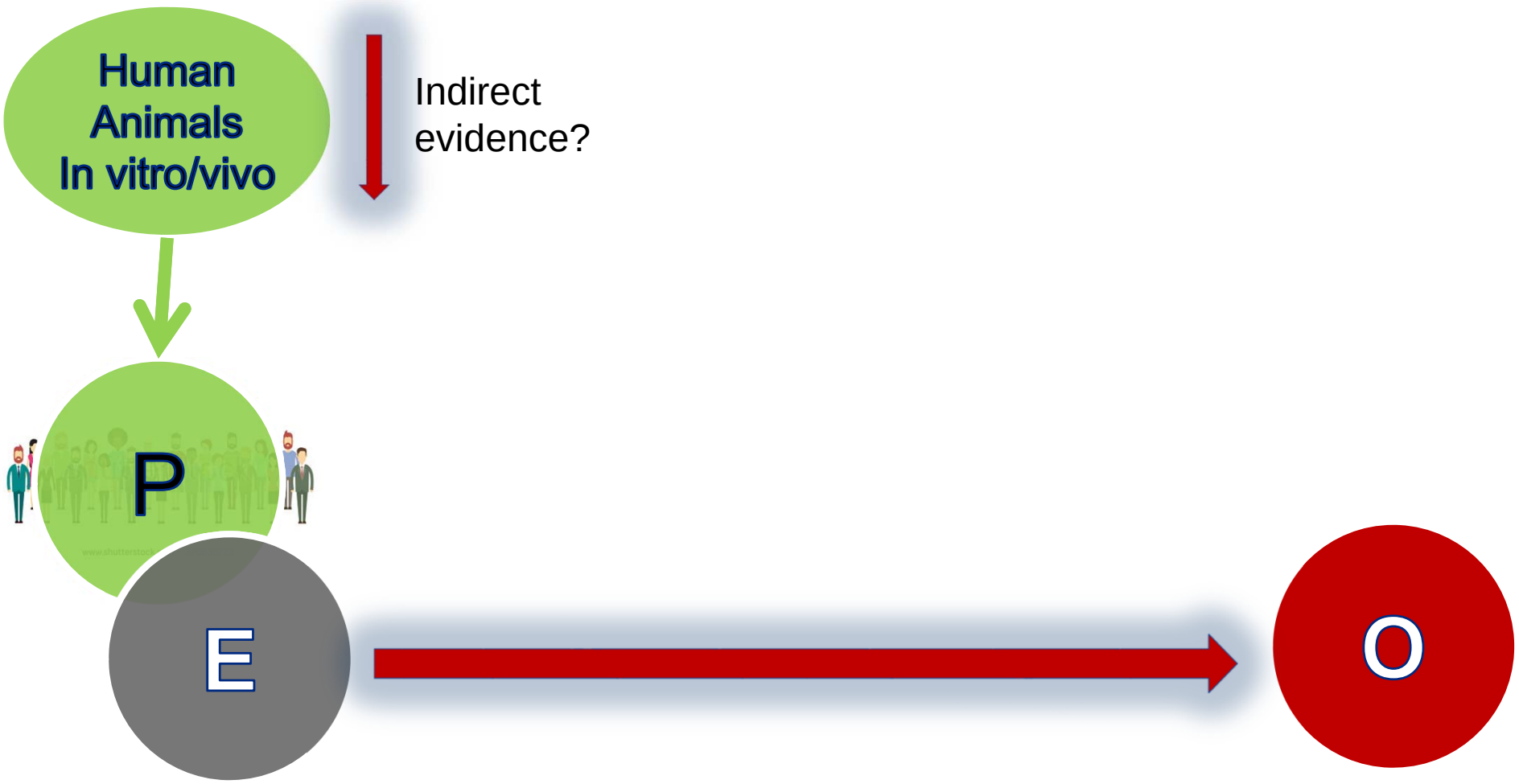
Five paradigmatic approaches and examples for identifying the exposure and comparator in systematic review and decision-making questions.


P

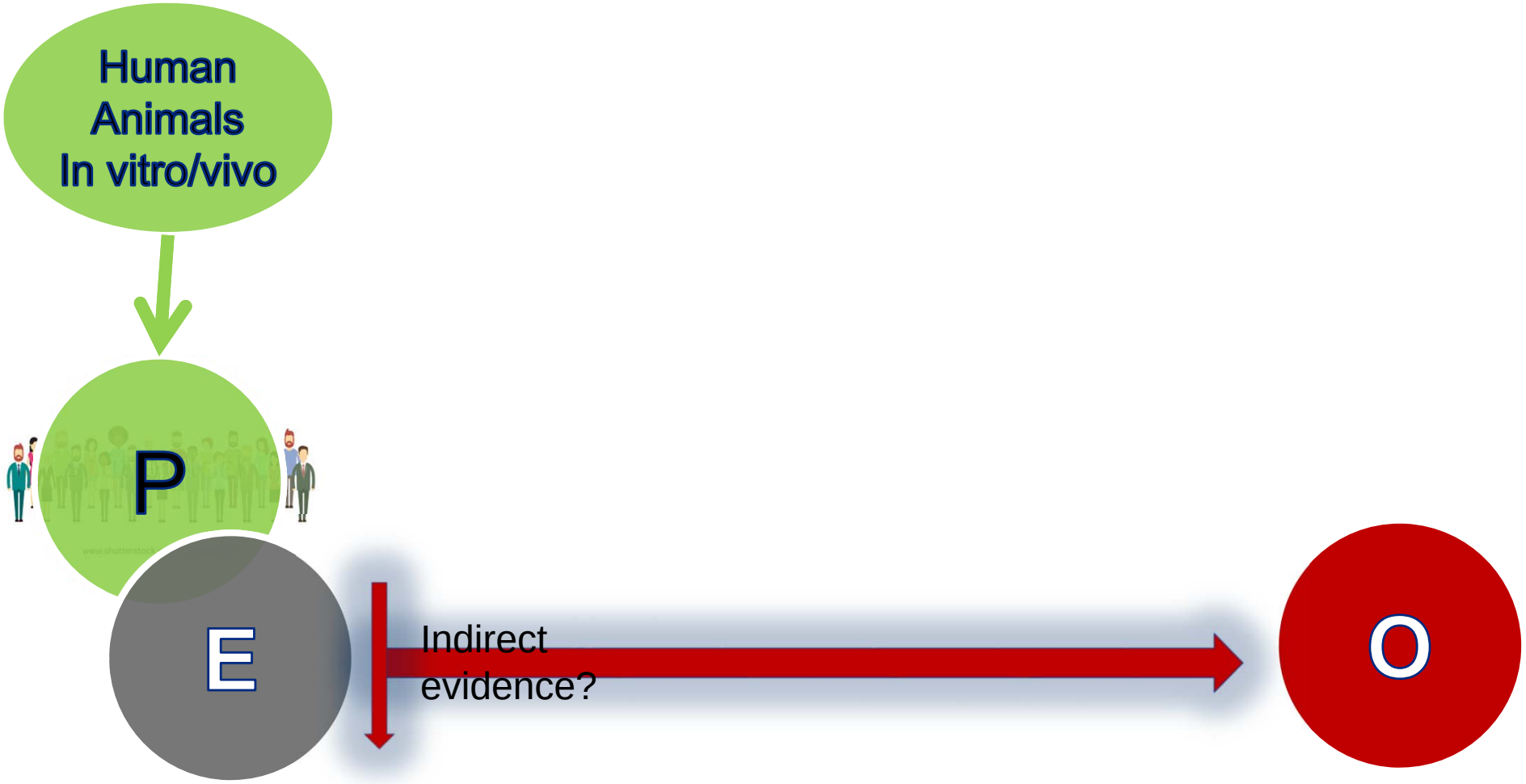

P
E


P
E
O

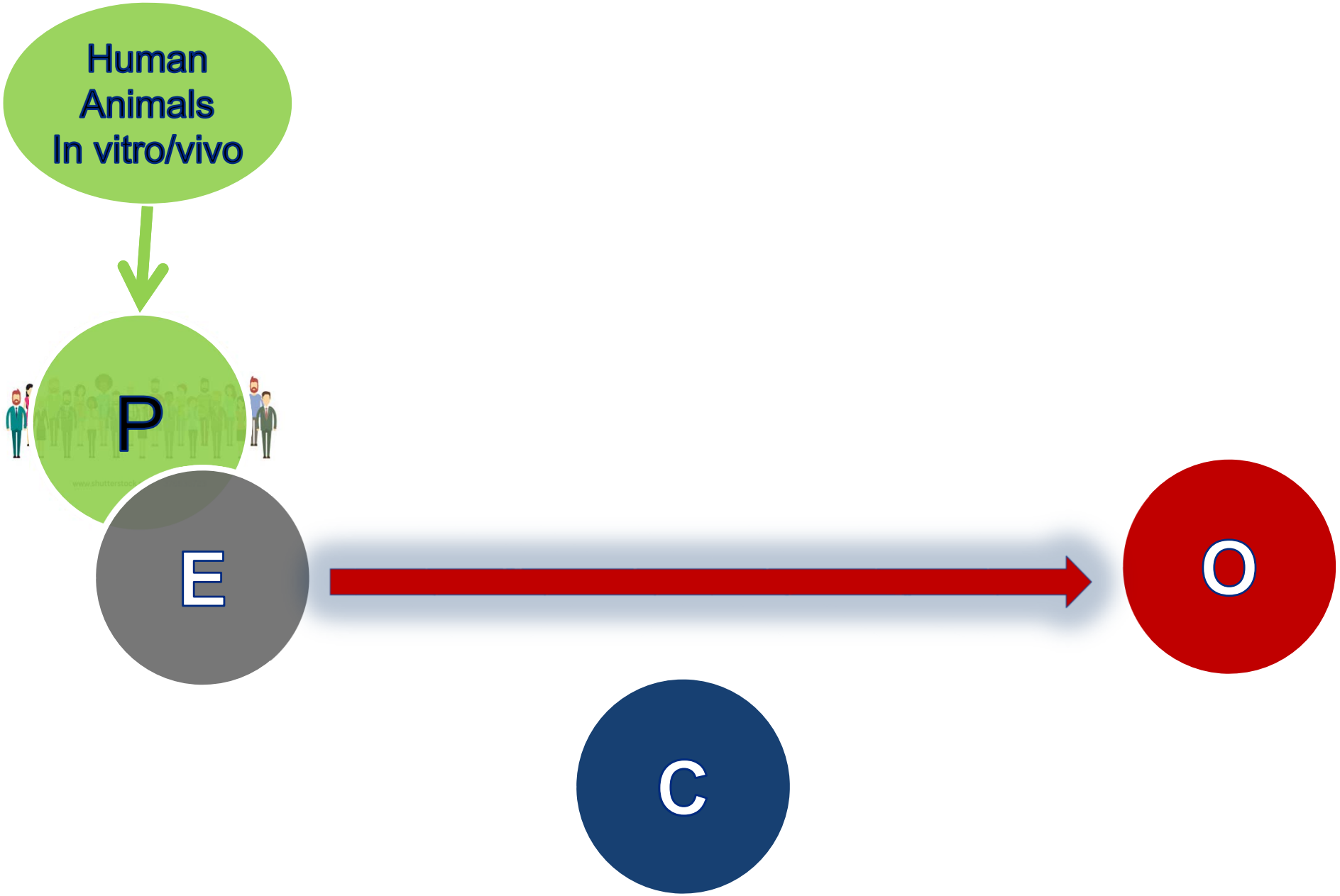

Human
Animals
In vitro/vivo
P
E
O

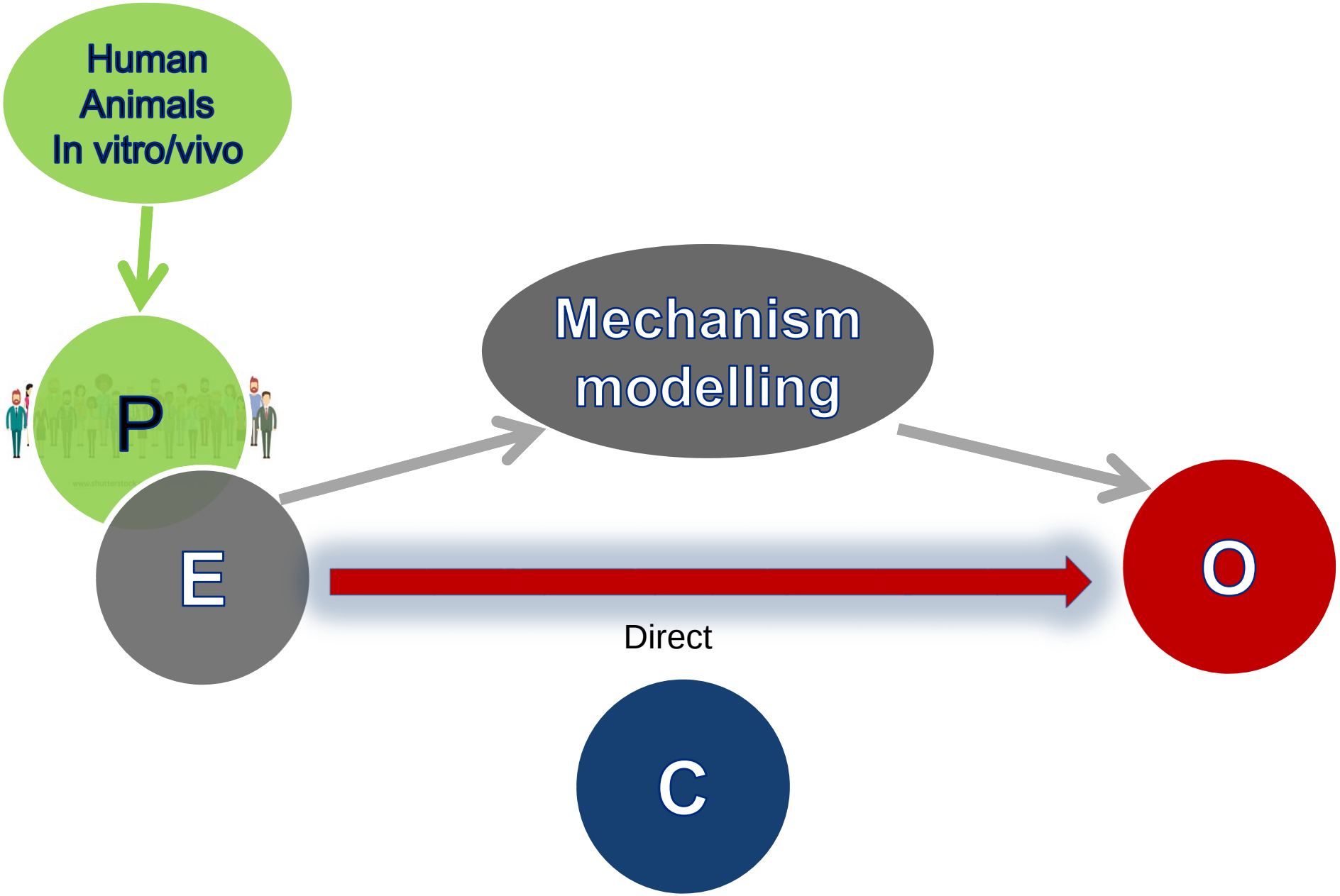

Human
Animals
In vitro/vivo
Indirect
evidence?
P
E
O

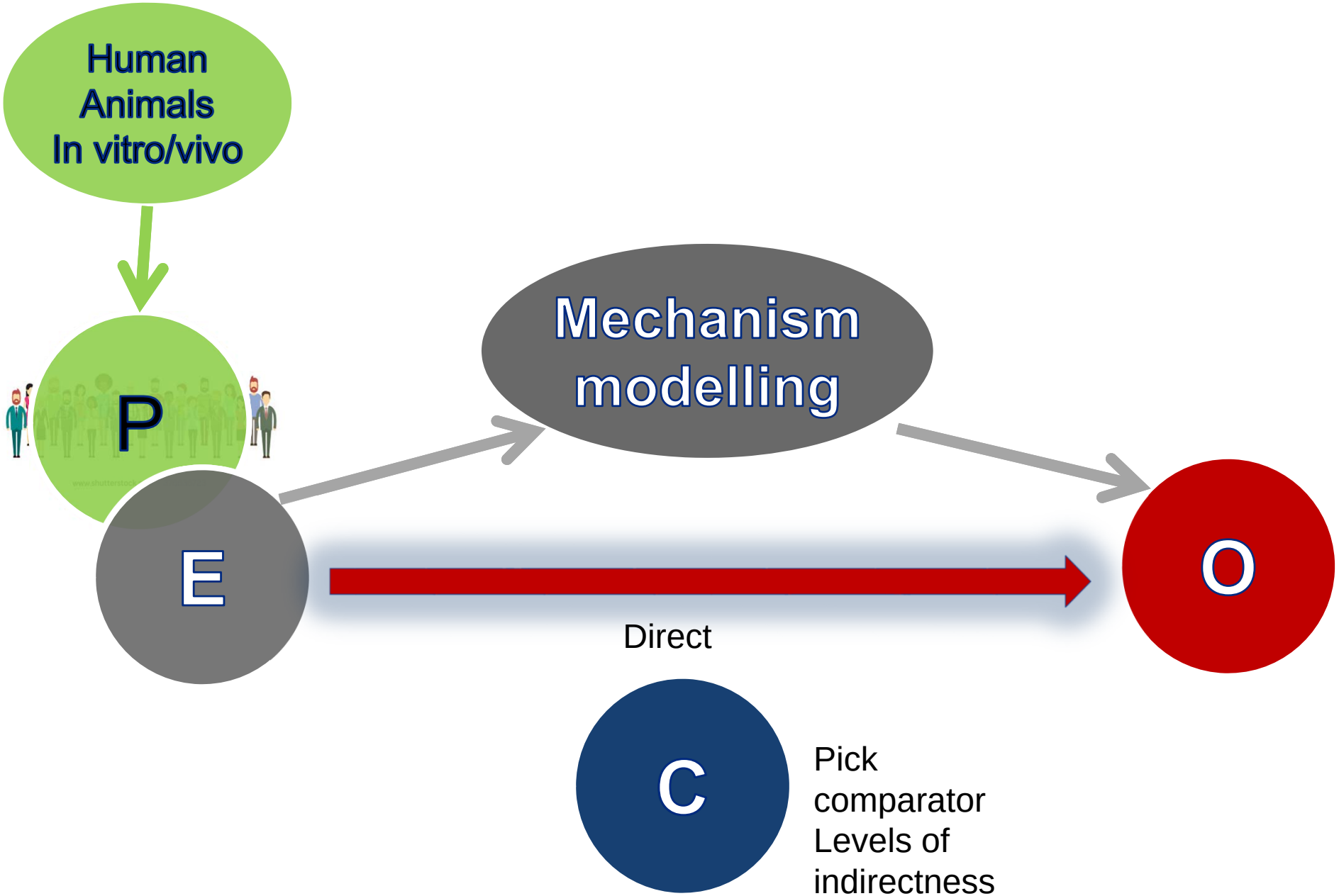

Human
Animals
In vitro/vivo
P
E
O

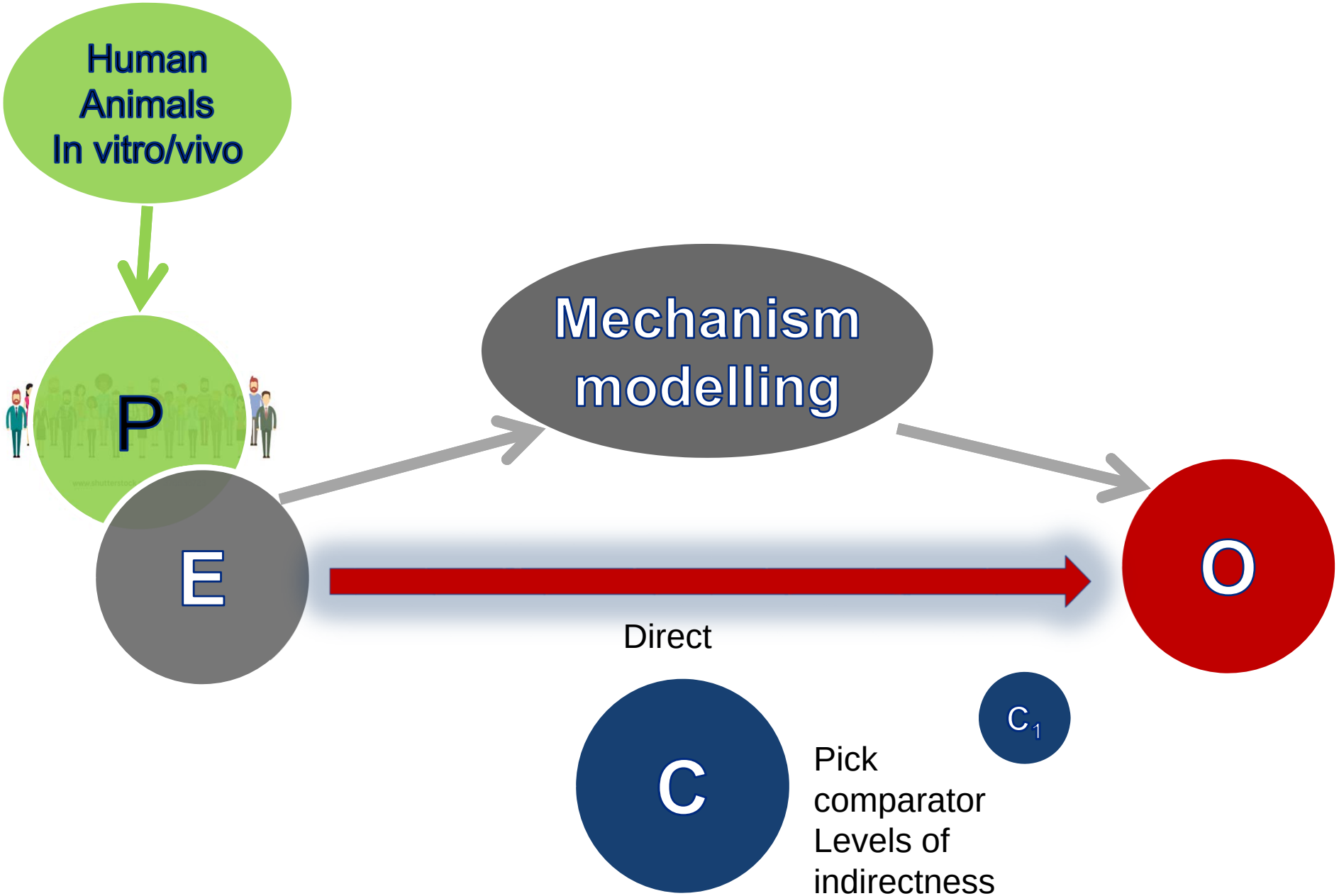

Human
Animals
In vitro/vivo
P
E
Indirect
evidence?
O

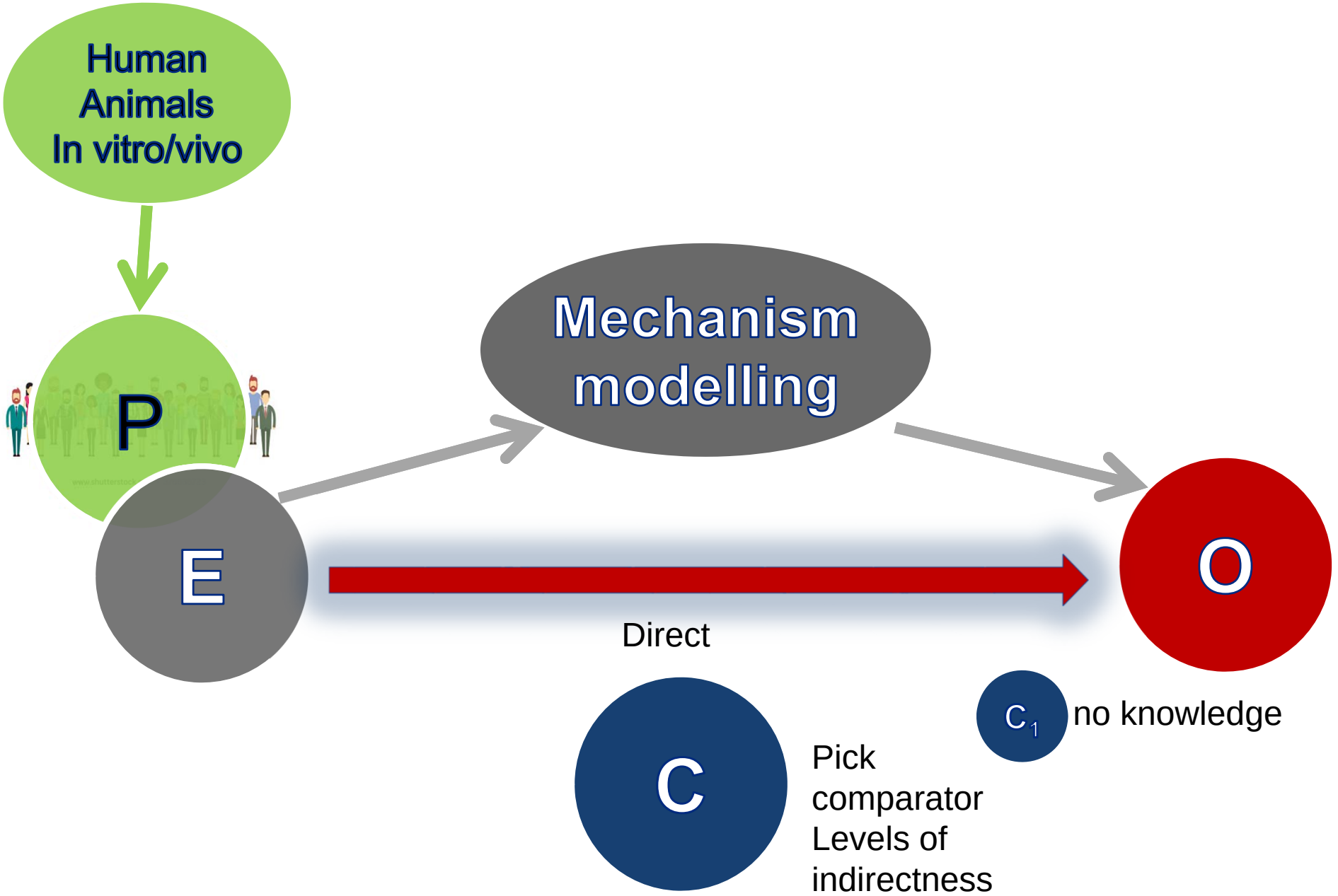

Human
Animals
In vitro/vivo
P
E
O

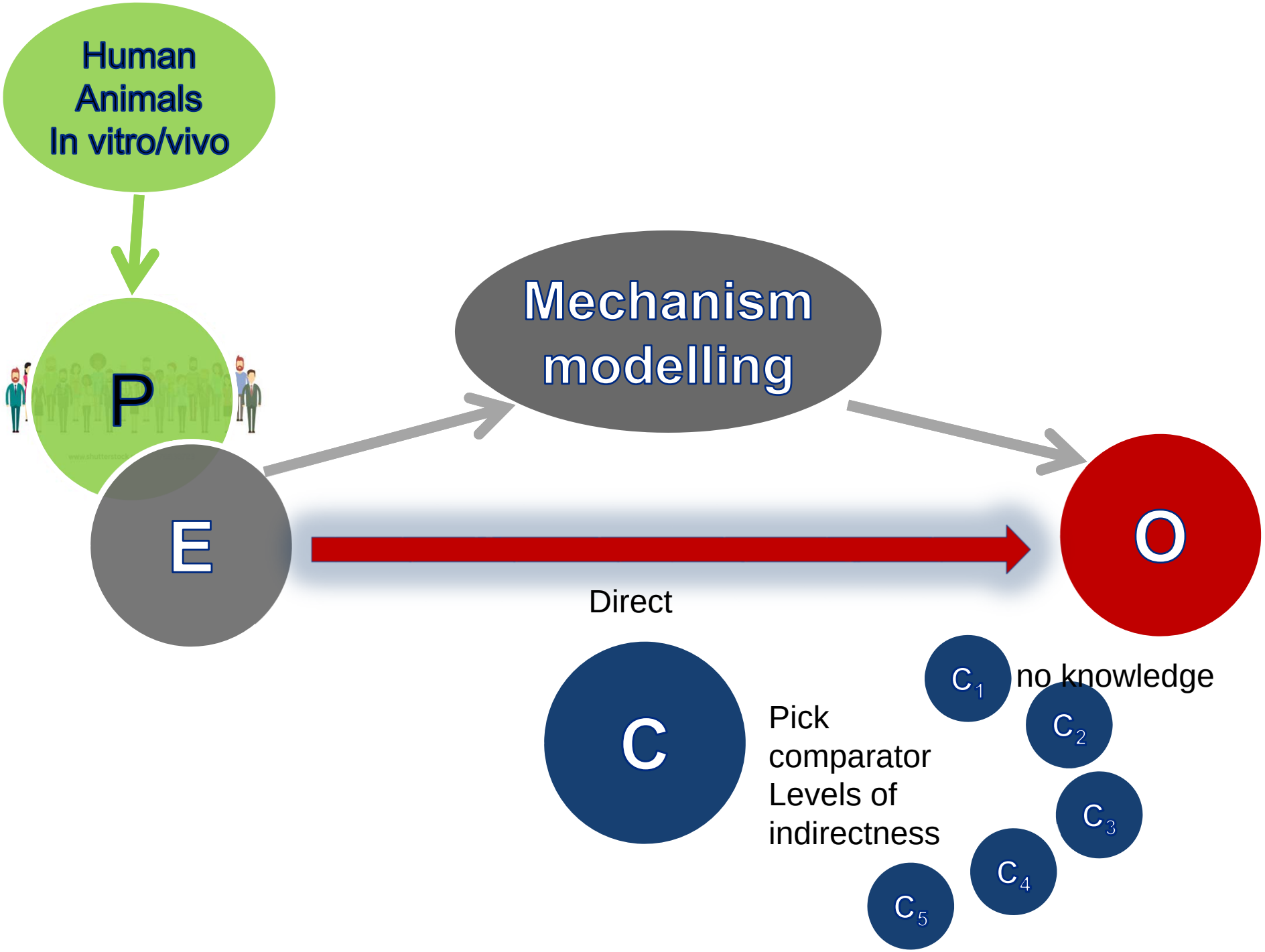

Human
Animals
In vitro/vivo
P
E
O
C

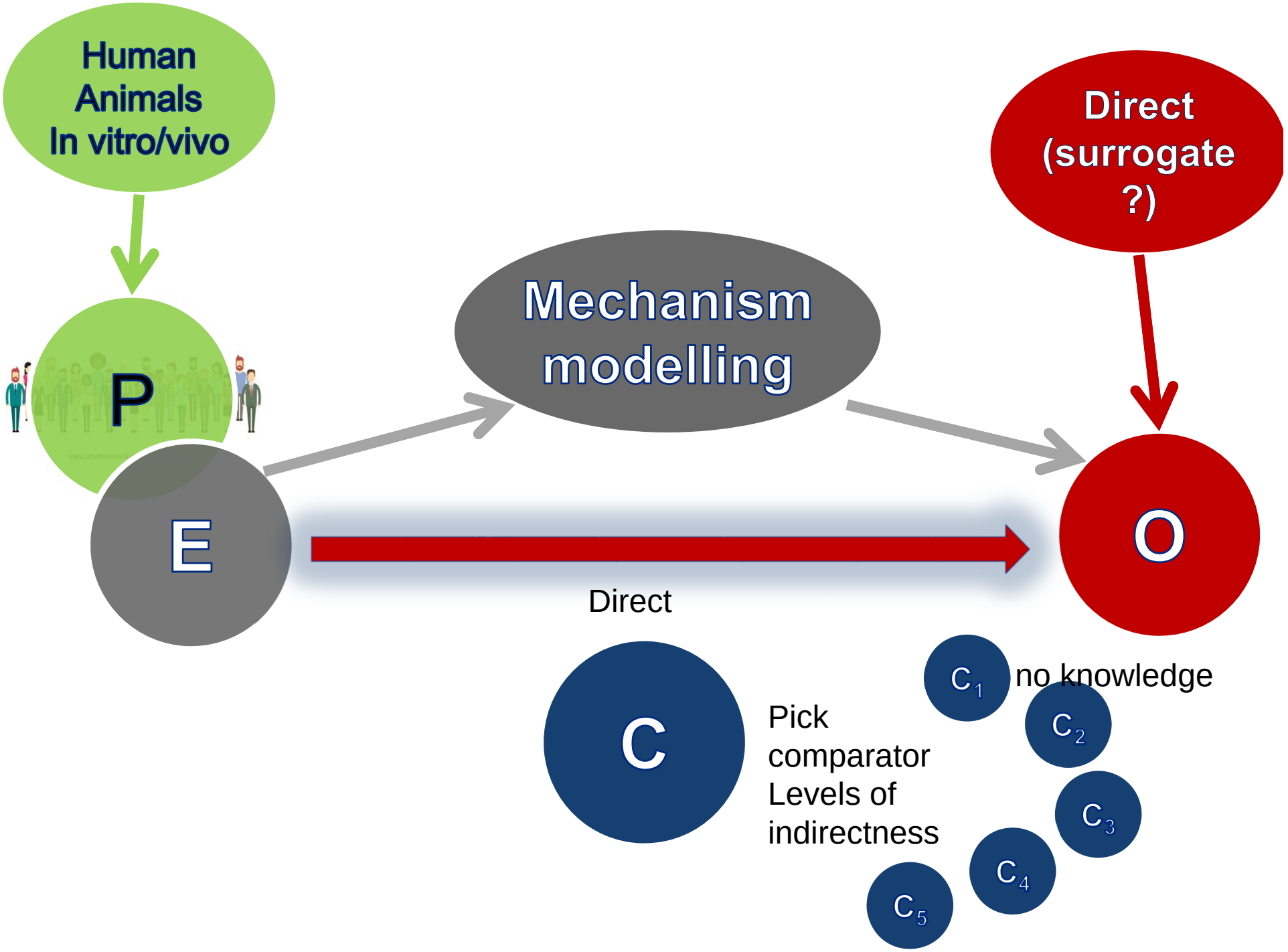

Human
Animals
In vitro/vivo
P
Mechanism
modelling
E
O
Direct
C

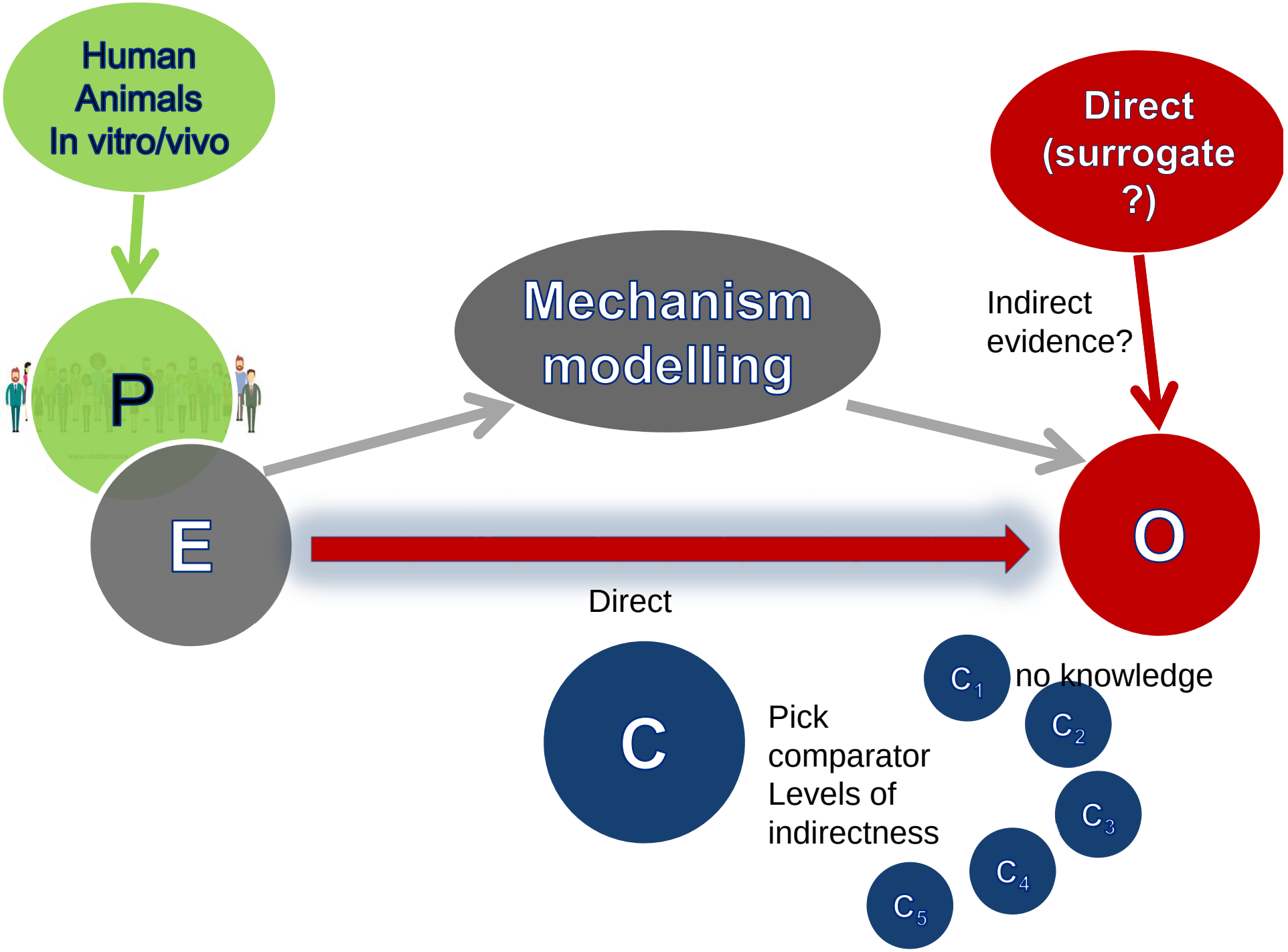

Human
Animals
In vitro/vivo
P
Mechanism
modelling
E
O
Direct
C
Pick
comparator
Levels of
indirectness

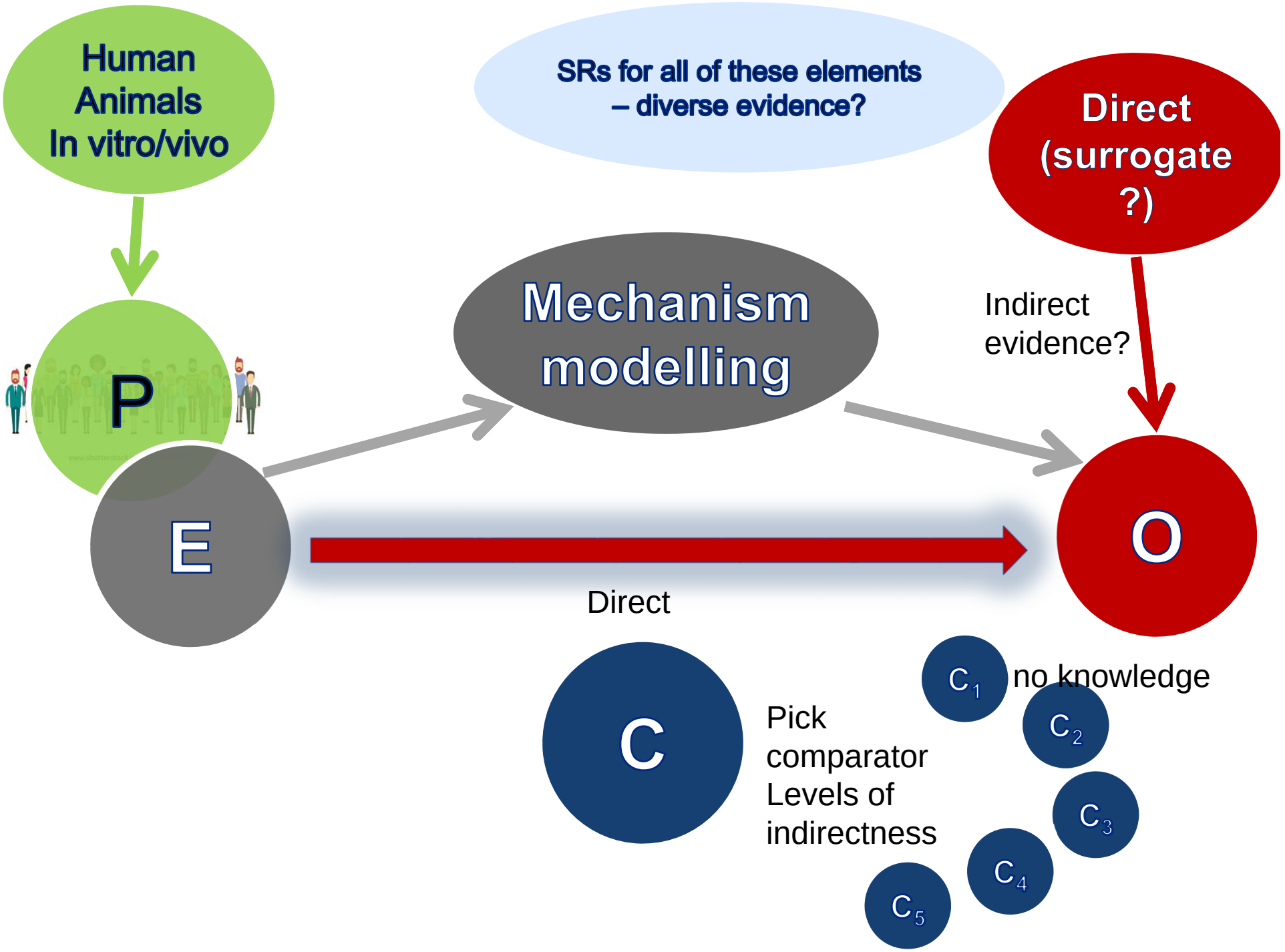

Human
Animals
In vitro/vivo
P
Mechanism
modelling
E
O
Direct
C
C1
Pick
comparator
Levels of
indirectness

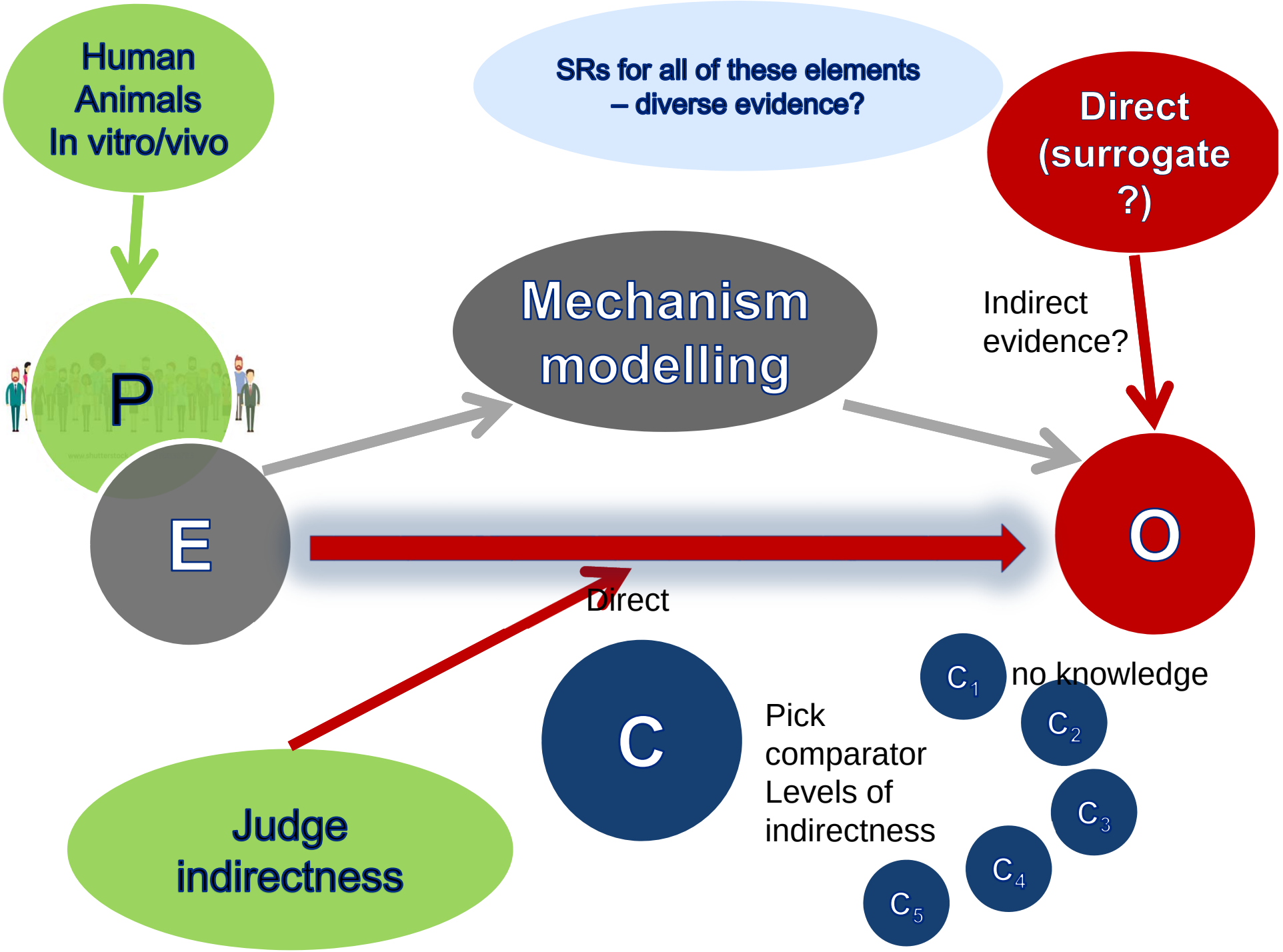

Human
Animals
In vitro/vivo
P
Mechanism
modelling
E
O
Direct
C
C1
no knowledge
Pick
comparator
Levels of
indirectness


Human
Animals
In vitro/vivo
P
E
Mechanism
modelling
O
Direct
C
Pick
comparator
Levels of
indirectness
C1
no knowledge
C2
C3
C4
C5


Human
Animals
In vitro/vivo
Direct
(surrogate
?)
Mechanism
modelling
P
E
O
Direct
C
Pick
comparator
Levels of
indirectness
C1
no knowledge
C2
C3
C4
C5


Human
Animals
In vitro/vivo
Direct
(surrogate
?)
Mechanism
modelling
Indirect
evidence?
P
E
O
Direct
C
Pick
comparator
Levels of
indirectness
C1
no knowledge
C2
C3
C4
C5


Human
Animals
In vitro/vivo
SRs for all of these elements
– diverse evidence?
Direct
(surrogate
?)
Mechanism
modelling
Indirect
evidence?
P
E
O
Direct
C
Pick
comparator
Levels of
indirectness
C1
no knowledge
C2
C3
C4
C5


Human
Animals
In vitro/vivo
SRs for all of these elements
– diverse evidence?
Direct
(surrogate
?)
Mechanism
modelling
Indirect
evidence?
P
E
O
Direct
C
Judge
indirectness
Pick
comparator
Levels of
indirectness
C1
no knowledge
C2
C3
C4
C5

Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

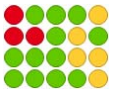
3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient

Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty



1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient

Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low

2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

3 factors can increase certainty

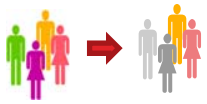
1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient

Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias



3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient

Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient

Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient

Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient

Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient

Determinants of certainty in a body of evidence: GRADE

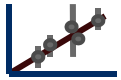
A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient



Determinants of certainty in a body of evidence: GRADE

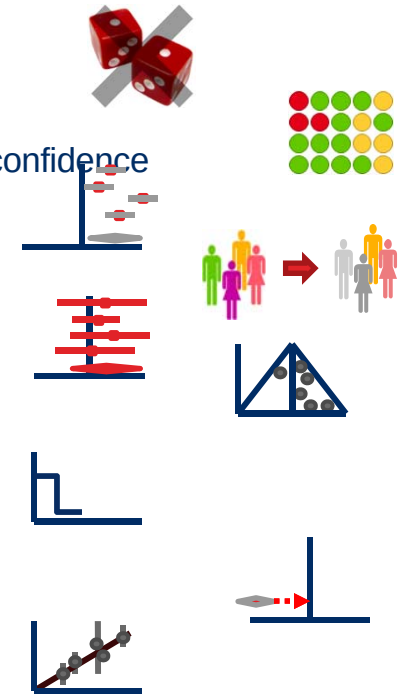
A body of evidence starts as: high | ⊕⊕⊕⊕

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision
5. Publication bias

3 factors can increase certainty

1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient



GRADE and Rapid Response

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Preface

Using GRADE to respond to health questions with different levels of urgency

Kristina A. Thayer [a], Holger J. Schünemann [b,*]

[a] Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, P.O. Box 12233, Mail Drop K2-02, Research Triangle Park, NC 27709, USA
[b] Department of Clinical Epidemiology & Biostatistics, Department of Medicine, McMaster University, Health Sciences Centre, Room 2C14, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

ARTICLE INFO

Article history:
Received 15 March 2016
Received in revised form 21 March 2016
Accepted 21 March 2016
Available online 26 April 2016

ABSTRACT

Increasing interest exists in applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health evidence. While ideally applied to evidence synthesized in systematic reviews and corresponding summary tables, such as evidence profiles, GRADE's correct application requires that "the evidence that was assessed and the methods that were used to identify and appraise that evidence should be clearly described." In this article, we suggest that GRADE could be applied to evidence assembled from narrative reviews, modelled (indirect) evidence, or evidence assembled as part of a rapid response, if the underlying judgments about the certainty in this evidence are based on the relevant GRADE domains and provided transparently. Health questions that require assessing the certainty in a body of evidence to provide trustworthy answers may range from hours, to days or weeks, to a few months to scenarios that allow assessing evidence without short-term time pressures. Time frames of emergent, urgent or rapid evidence assessments will often require relying on existing summaries or rapidly compiling the available evidence and making assessments. Even without available full systematic reviews, expressing the certainty in the evidence can provide useful guidance for users of the evidence and those who evaluate certainty in effects. The ratings also help clarifying disagreement between organizations tackling similar questions about the evidence. Using the structured GRADE domains, narrative or other summaries of the evidence can be presented transparently.

GRADE and Rapid Response

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/en

Preface

Using GRADE to respond to health questions with different leve

Kristina A. Thayer [a], Holger J. Schünemann [b,*]

[a] Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Depa
Mail Drop K2-02, Research Triangle Park, NC 27709, USA
[b] Department of Clinical Epidemiology & Biostatistics, Department of Medicine, McMaster University, Health Sciences Centre, Room 2C

ARTICLE INFO

Article history:
Received 15 March 2016
Received in revised form 21 March 2016
Accepted 21 March 2016
Available online 26 April 2016

ABSTRACT

Increasing interest exists in applying the Grading of Recommen
(GRADE) approach to environmental health evidence. While i
atic reviews and corresponding summary tables, such as evide
that "the evidence that was assessed and the methods that v
should be clearly described." In this article, we suggest that
from narrative reviews, modelled (indirect) evidence, or evid
underlying judgments about the certainty in this evidence are
ed transparently. Health questions that require assessing the c
thy answers may range from hours, to days or weeks, to a few
without short-term time pressures. Time frames of emergent, u
quire relying on existing summaries or rapidly compiling the
without available full systematic reviews, expressing the certa
for users of the evidence and those who evaluate certainty in ef
between organizations tackling similar questions about the evi
rative or other summaries of the evidence can be presented tr

Table 1
Examples of GRADE applied across different time scenarios.

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Example	West Virginia Elk River spill Population: community exposed to the chemical spill. Intervention/exposure: chemicals in the spill that contaminated water supply. Comparison: no chemicals in the spill. Outcomes: genotoxicity, developmental or reproductive toxicity, liver toxicity and others.	Melamine in composite food products Population: healthy people Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day. Comparison: higher than 0.5 mg/kg body weight of melamine from composition food. Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).	Avian influenza Population: people with suspected avian influenza infection. Intervention/exposure: oseltamivir. Comparison: no oseltamivir. Outcomes: mortality, duration of hospitalization, incidence of lower respiratory tract complications (used for this example of the certainty assessment below), antiviral drug resistance existing before treatment, and serious adverse events.	PFOA and birth weight Population: women of reproductive age and fetuses (before and/or during pregnancy or development). Intervention/exposure: perfluorooctanoic acid (PFOA; CAS# 335-67-1) or its salts. Comparison: lower levels of PFOA. Outcomes: fetal growth, birth weight, other measures of fetal or newborn size.
Type of evidence	Available evidence: animal toxicology studies in rodents for two chemicals in the spill (a 28-day study and a teratology study) and SAR analyses for other chemicals in the spill with no toxicology data.	Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.	Available evidence: five randomized trials in patients with seasonal flu (summarized in systematic reviews), case studies of patients with avian influenza, *in vitro* and *in vivo* animal data.	Available evidence: a systematic review of 18 non-randomized (observational) studies (10 were included in a meta-analysis).
GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments (note these are not necessarily reflecting judgments in the original scenarios).				
Risk of bias	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals were accounted for). Ideally, RoB assessments would be available for individual studies and summarized across studies. In the Elk River example, the number of animal studies was small and could be assessed at the individual level within a short-time frame. A de novo risk of bias evaluation may not be feasible in cases where evidence is drawn from existing narrative risk assessments that summarize a large body of literature. Nevertheless, it may still be possible to assess risk of bias based on the uncertainties and evidence limitations described in the risk assessment. SAR: could be assessed using OECD model validation or similar guidance that recommends presentation of a defined domain of applicability for a defined endpoint supported by appropriate measures of goodness-of-fit (OECD, 2007).	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, pathologists blinded in their assessments or all animals accounted for). In this case it appears that the animal studies did not report that it was randomized and, thus, may be at risk of bias.	Not serious	Serious based on some concern of risk of bias in the included studies (in the original report, the authors used an approach to rating certainty that accounted for risk of bias by lowering the certainty from high to moderate).
Imprecision	Could be assessed for both animal data and SAR (e.g., considering statistical or numerical uncertainty in model parameters).	While no summary estimates are available, an assessment could be guided by the availability of data from only 100 animals in different exposure groups which would result in wide confidence intervals.	Serious	Not serious
Inconsistency	Could be assessed for both animal data and SAR (e.g., assessing similarity of results based on applying different models).	Only one study was included and therefore no inconsistency is present (Guyatt et al., 2011d).	Not serious	Not serious
Publication bias	Could be assessed for both animal studies and SAR. A judgment of undetected might be reasonable if	Could be assessed using guidance for animal studies but a judgment of undetected might be reasonable if	Undetected	Undetected

Table 1
Examples of GRADE applied across different time scenarios.

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Example	West Virginia Elk River spill Population: community exposed to the chemical spill. Intervention/exposure: chemicals in the spill that contaminated water supply. Comparison: no chemicals in the spill. Outcomes: genotoxicity, developmental or reproductive toxicity, liver toxicity and others.	Melamine in composite food products Population: healthy people Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day. Comparison: higher than 0.5 mg/kg body weight of melamine from composition food. Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).	Avian influenza Population: people with suspected avian influenza infection. Intervention/exposure: oseltamivir. Comparison: no oseltamivir. Outcomes: mortality, duration of hospitalization, incidence of lower respiratory tract complications (used for this example of the certainty assessment below), antiviral drug resistance existing before treatment, and serious adverse events.	PFOA and birth weight Population: women of reproductive age and fetuses (before and/or during pregnancy or development). Intervention/exposure: perfluorooctanoic acid (PFOA; CAS# 335-67-1) or its salts. Comparison: lower levels of PFOA. Outcomes: fetal growth, birth weight, other measures of fetal or newborn size.
Type of evidence	Available evidence: animal toxicology studies in rodents for two chemicals in the spill (a 28-day study and a teratology study) and SAR analyses for other chemicals in the spill with no toxicology data.	Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.	Available evidence: five randomized trials in patients with seasonal flu (summarized in systematic reviews), case studies of patients with avian influenza, *in vitro* and *in vivo* animal data.	Available evidence: a systematic review of 18 non-randomized (observational) studies (10 were included in a meta-analysis).
GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments (note these are not necessarily reflecting judgments in the original scenarios).				
Risk of bias	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, pathologists blinded in their assessments or all animals accounted for). In this case it	Not serious	Serious based on some concern of risk of bias in the included studies (in the original report, the authors used an approach to rating certainty that accounted for risk of bias by lowering the certainty from high to

Table 1
Examples of GRADE applied across different time scenarios.

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Example	West Virginia Elk River spill Population: community exposed to the chemical spill. Intervention/exposure: chemicals in the spill that contaminated water supply. Comparison: no chemicals in the spill. Outcomes: genotoxicity, developmental or reproductive toxicity, liver toxicity and others.	Melamine in composite food products Population: healthy people Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day. Comparison: higher than 0.5 mg/kg body weight of melamine from composition food. Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).	Avian influenza Population: people with suspected avian influenza infection. Intervention/exposure: oseltamivir. Comparison: no oseltamivir. Outcomes: mortality, duration of hospitalization, incidence of lower respiratory tract complications (used for certainty antiviral before tr adverse e	PFOA and birth weight Population: women of reproductive age and fetuses (before and/or during pregnancy or development). Intervention/exposure: perfluorooctanoic acid (PFOA; CAS# 335-67-1) or its salts. Comparison: lower levels of PFOA. l or
Type of evidence	Available evidence: animal toxicology studies in rodents for two chemicals in the spill (a 28-day study and a teratology study) and SAR analyses for other chemicals in the spill with no toxicology data.	Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.	Available trials in p (summar reviews), with avia *in vivo* ar	tic ere
GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judg				*he original scenarios).*
Risk of bias	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, pathologists blinded in their assessments or all animals accounted for). In this case it	Not serio	n of dies hors rtainty by igh to

Rest of table summarizes:

- GRADE domains
  - risk of bias, imprecision, indirectness, inconsistency, publication bias, magnitude, etc.
- Certainty in evidence
- Possible summary statements

GRADE project groups

Feel free to join

- Environmental Health
- Modelling
- Public Health

Distinguish

Association (GRADE for risk factors)

Causality

Interventions

Decisions

Population: People

Intervention: Regulation to ban/reduce to certain level

Comparison: no regulation

Outcomes: cancer, road safety (ethylene glycol), surgical infections

PICO

GRADE Evidence to Decision (EtD) framework

Can help decision makers move from evidence to a recommendation or decision by:

- **Informing judgements about the pros and cons of each option**
- **Considering each important factor that determine a decision (criteria)**
- **Providing a concise summary of the best available research evidence to inform judgements**
- **Helping to structure discussion and identify reasons for disagreements**
- **Making the basis for decisions transparent and adaptable for target audiences:**
  - **Clinical and public health**
  - **Policy making**
  - **Health systems**
  - **Coverage decisions**

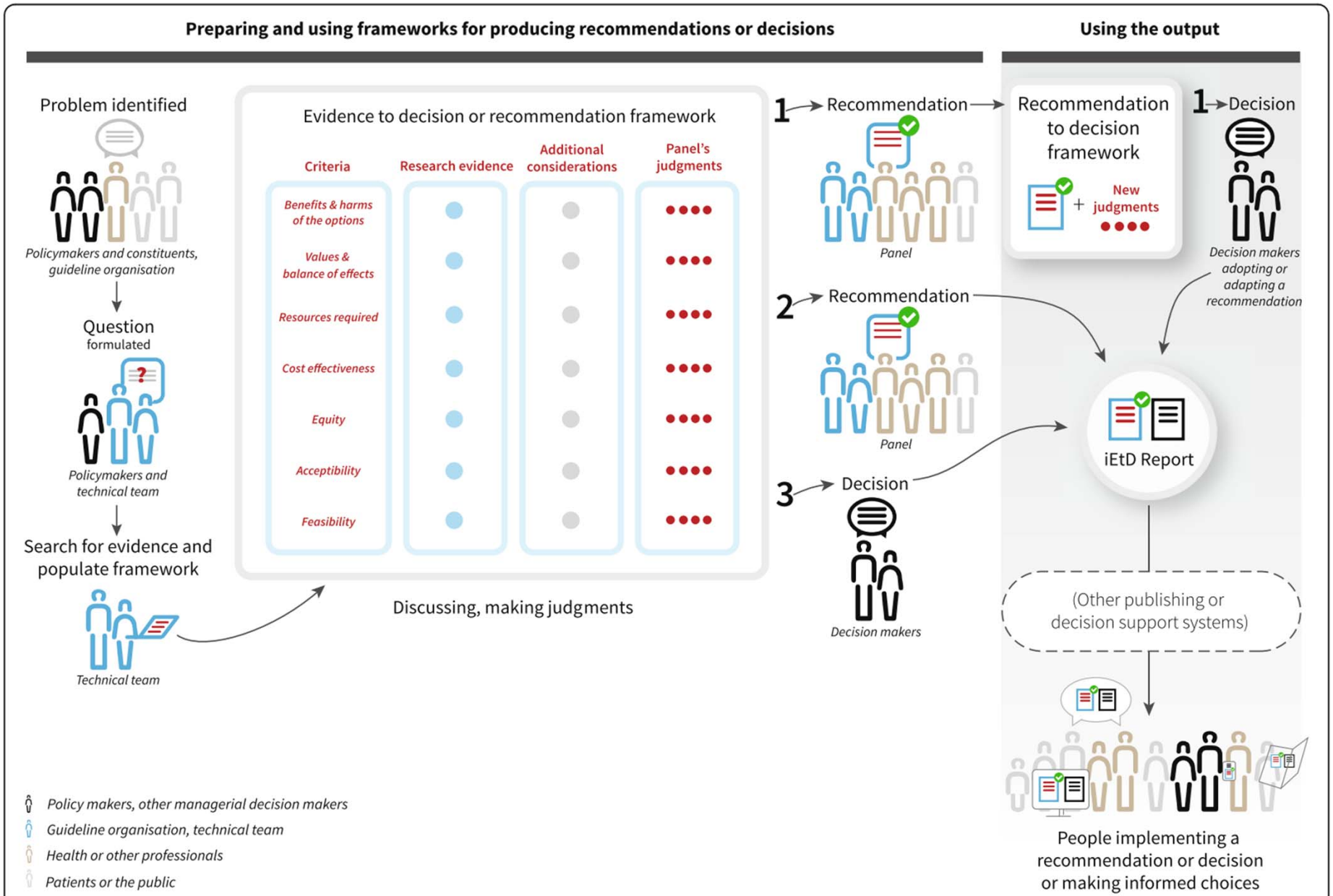


Fig. 1 Evidence to Decision (EtD) conceptual map workflow

Moberg *et al. Health Research Policy and Systems* (2018) 16:45
https://doi.org/10.1186/s12961-018-0320-2

Thank you

 @schunemann_mac